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<p>(54) Title: IMPROVED IONTOPHORETIC RESERVOIR APPARATUS</p> <p>(57) Abstract</p> <p>The invention provides a device for the iontophoretic administration of an ionized substance. The device includes: (a) a current distributing member (31); (b) an electrolyte reservoir (32) containing an electrolyte, in electrical communication with the current distributing member (31); (c) an ionized substance reservoir (35) containing an ionized or ionizable substance (37), in ionic communication with the electrolyte reservoir (32) and adapted to be placed in ionic communication with an epithelial surface (38); and (d) ion regulating means (39) positioned between the current distributing member (31) and the ionized substance reservoir (35) for capturing electrochemically generated anions and/or cations. The electrolyte reservoir (32) includes a polymeric matrix (33) for retaining the ion regulating means (39) and substantially inhibiting migration of the ionized or ionizable substance into the electrolyte reservoir (35). During application of an electrical potential migration of electrochemically generated ions between the current distributing member (31) and the ionized substance reservoir (35) is substantially prevented, and iontophoretic delivery of the substance from the ionized substance reservoir (35) through said epithelial surface (38) is effected. The invention further provides multifunctional reservoir apparatus for use in iontophoretic devices. The multifunctional reservoir apparatus is adapted to receive a current distributing member and can regulate either cations or anions for use in either anodal or cathodal administration of ionized substances.</p>		

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IMPROVED IONTOPHORETIC RESERVOIR APPARATUS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to apparatus for the iontophoretic delivery of ionized or ionizable substances across an epithelial surface.

2. Background of the Related Art

Transdermal drug delivery systems have, in recent years, become an increasingly important means of administering drugs. Such systems offer advantages clearly not achievable by other modes of administration, such as avoiding introduction of the drug through the gastrointestinal tract or punctures in the skin, to name a few.

Presently, there are two types of transdermal drug delivery systems, i.e., "passive" and "active." Passive systems deliver drug through the skin of the user unaided, an example of which would involve the treatment of angina with topical application of nitroglycerin. Active systems, on the other hand, deliver drug through the skin of the user assisted by electrical energy (iontophoresis) or ultrasound energy (phonophoresis). Iontophoresis, according to Stedman's Medical Dictionary, is defined as "the introduction into the tissues, by means of an electric current, of the ions of a chosen medicament." There has been considerable interest in iontophoresis to perform delivery of drugs for a variety of purposes.

Conventional iontophoretic devices, for delivering a drug or medicine transdermally through iontophoresis, basically consist of two electrodes, i.e., an anode

and a cathode. Such devices are disclosed in U.S. Patent Nos. 4,820,263 to Spevak et al., 4,927,408 to Haak et al., and 5,084,008 to Phipps, the disclosures of which are hereby incorporated by reference. Usually, electric current is provided from an external supply at the anode, and back out at the cathode.

A number of constraints limit the design of a high dose efficient iontophoretic patch, where dose efficiency is defined as the fraction of the loaded dose which is administered. These constraints include:

- a) providing enough "electrochemical fuel" for the electrochemistry of electron to ion conversion at the metal/water interface;
- b) keeping the active agent solution at a pH at which there is no skin irritation and no active agent deterioration, and at which the charge on the active agent is favorable for iontophoretic delivery;
- c) keeping the concentration of the other ions of the same charge as the active agent at a low enough concentration so that they do not compete for the current to an extent that the transport number of the active agent is significantly reduced; and
- d) keeping the volume of the active agent reservoir low so that the mass of active agent is low, to obtain high dose efficiency, while keeping the concentration of the active agent high to enhance the current efficiency. Unfortunately, when the active agent reservoir volume is kept low, but the mass of fuel ion and its counter ion is kept constant, the concentrations of the fuel ion and counter ion increase, aggravating the competing ion problem.

Potential solutions to this problem have been described. Typically, these solutions describe a membrane between an upper reservoir and lower reservoir, restricting the migration of certain species of ions. For example, an ion exchange membrane, either cationic or anionic, has been described in U.S. Patent Nos. 4,722,726 to Sanderson et al., 4,927,408 to Haak et al., and 5,006,108 to LaPrade, as well as in

European Patent document EP 0 318 776 A1 to Tapper et al. Alternatively, a size exclusion membrane has been described in U.S. Patent Nos. 5,084,008 to Phipps and 4,731 049 to Parsi.

In U.S. Patent No. 5,084,008 to Phipps, an anodal system is described which uses an anionic exchange membrane between a drug reservoir and an electrolyte reservoir. In this device, the electrode material is silver, and the fuel ions (Cl^-) freely pass through the membrane to react with the silver. However, the silver ions (Ag^+) are blocked by the membrane. The pH in the upper reservoir is unaltered because the classical electrochemical reaction:



does not involve electrolysis of water and so avoids the generation of H^+ and OH^- ions. To promote conductivity, some level of electrolyte is present in both the upper and lower reservoirs. $\text{Na}^+ \text{Cl}^-$ is a typical electrolyte.

In accounting for current in this model, 100% of the current is converted at the silver electrode, by means of either of the following reactions:



or



In this configuration, none of the Ag^+ ions can appear in the lower reservoir because of the anion exchange character of the membrane. Instead, 100% of the current is carried by Cl^- ions migrating toward the electrode. Electroneutrality is maintained: 100% of the current enters the device as Ag^+ ions, while 100% of the current crosses the membrane as Cl^- ions entering the upper reservoir.

In the lower reservoir in this model, the drug to be delivered is present as a cation (D^+) plus its counter ion, typically Cl^- . When this is the only electrolyte, and

its concentration (molarity) is low, as is necessary with peptides because of the high molecular weights involved, skin irritation can be observed. Dramatic drops in the pH of the lower reservoir, and very low current efficiency for transport of the drug, can also be observed. Therefore, while an anion exchange membrane appears workable in concept, in practice it results in skin irritation and low drug delivery.

One way to reduce the skin irritation and reduce the pH drop is to add Na^+Cl^- to the lower reservoir. The Na^+ ions compete for current with the Cl^- ions from the skin and with the drug, but to a lesser extent than the competition provided by the available protons (H^+). Unfortunately, the Na^+Cl^- concentration is not stable in the reservoir, but decreases with current. One hundred percent (100%) of the current out of the electrolyte reservoir is carried by Cl^- ions leaving the lower reservoir, but the current across the skin is made up of Na^+ and D^+ ions leaving the device, as well as Cl^- ions entering the device. Thus, the NaCl in the lower reservoir is depleted during operation. At physiological concentrations (150 mM), roughly 50% of the current across the skin can be expected to be carried by Na^+ ions exiting the reservoir, while the other 50% of the current is carried by Cl^- ions entering the reservoir. In the case of peptide drugs, the amount of current-carrying drug (D^+) leaving the reservoir is typically less than about 1%. If enough saline is placed in the lower reservoir to run at the typical currents, then the Na^+Cl^- molar concentration required may exceed 1 M. In this case, competition for current between the electrolyte ions and the D^+ ions is prohibitively high. The Phipps et al. design, might operate when there is an adequate source of Cl^- ions in the lower reservoir and when delivery of the active ingredient (preferably the drug hydrochloride salt) does not have to be particularly dose efficient. However, when high dose efficiency is desired from a relatively low molar concentration of active ingredient, this concept cannot be expected to be effective.

In concept, a way to cure the problem of Na^+ ion depletion from the design having an anion exchange membrane would be to replace the anion exchange membrane with a cation exchange membrane. In such a case, the Ag^+ ions coming off the silver electrode pass through the upper reservoir, and cause release of Na^+ ions into the lower reservoir upon interaction with the upper surface of the membrane. Thus, instead of having 100% of the membrane current carried by Cl^- ions moving upward, 100% of the membrane current is now carried by Ag^+ ions exchanging with Na^+ ions, with the Na^+ ions entering the lower reservoir. Consequently, instead of the lower reservoir being depleted of NaCl , the concentration of NaCl increases with time. Moreover, just as occurs in the design using an anion exchange membrane, the result in this case is that too much Na^+ in the lower reservoir, which causes low current efficiency for the drug D^+ . In this latter case, the poorest current efficiency occurs at the end of the episode, while with the anion exchange concept, the poorest current efficiency occurs at the beginning of the episode.

An alternative concept to resolve these problems is to use a size exclusion membrane between the drug and electrolyte reservoirs, such as is also shown in the device disclosed in U.S. Patent No. 4,927,408 to Haak. The pore size of the size exclusion membrane is selected such that migration of the drug (D^+) from the lower reservoir into the upper reservoir is prevented, but the Na^+ and Cl^- ions can pass freely through the membrane. Thus, the lower reservoir can be made small to keep the mass of the drug low, but its concentration high. Concomitantly, the upper reservoir can be made relatively large so that enough Cl^- ions are available to handle the electrochemistry, while the concentration of Na^+ and Cl^- ions are kept relatively low. In this type of configuration, the Na^+ does not compete excessively with D^+ and does not significantly drop the current efficiency or transport number of D^+ .

This latter concept may provide an adequate solution, but can do so only as long

as the flow of current is kept low. To keep the Na^+ concentration above about 150 mM (i.e., physiological concentration) at higher currents, the upper reservoir must be made quite large. For example, in theory, using a current of 1.25 mA and 150 mM saline for drug delivery over 24 hours requires a reservoir almost an inch thick and tens of cm^2 in area. Such a device is prohibitively large.

Various other devices are known which also employ size selective membranes. Among these are a series of patent documents to Sibališ, including U.S. Patent Nos. 4,919,648 and 4,921,475. These documents disclose devices which require a size selective membrane pouch surrounding the drug reservoir to limit loss of the active agent. These devices also fail to teach or suggest means for effectively controlling ion migration.

Another concept to potentially resolve the problem of ion control involves using an ion exchange resin (e.g., resin beads) in one of the reservoirs of the iontophoretic device. While the electrochemically generated ions of the electrode material may be trapped in these beads, the result is exactly the same as the two cases of anion and cation exchange membranes discussed above; Na^+ is either depleted or generated in excessive amounts. Such an approach is exemplified by U.S. Patent No. 4,973,303 to Johnson et al., which discloses iontophoretic apparatus incorporating an ion exchange resin capable of buffering pH changes by sequestering electrolytically generated ions having the same charge sign as the drug. This patent does not, however, provide any teaching with regard to the control of ion concentration when pH changes are less critical, such as when sacrificial electrodes are employed and electrolysis of water is avoided. Nor does this patent teach or suggest that the drug might be prevented from contacting the current distributing member.

With all of the concepts described above, the problem with each proposed

solution is poor control of the ions having the same charge sign as the drug. These competing ions are either consumed too fast or generated too fast, thereby quickly degrading efficiency and significantly limiting the utility of the proposed devices. In contrast, it has been unexpectedly found that the iontophoretic device of the invention provides regulation of these similarly charged ions; where regulation is defined as the maintenance of relatively low, but substantially constant, concentrations of competing ions in the electrode. The essentially constant and low concentration of competing ions in the present invention allows the construction of relatively small iontophoretic devices having high current efficiency and operating over extended periods of time, as well as enabling these devices to have high dose efficiencies.

Various other considerations which bear on the design of iontophoretic apparatus have been studied. For example, U.S. Patent No. 4,744,787 to Phipps et al. discloses an iontophoretic device requiring a sacrificial electrode material to prevent electrolysis of water during drug delivery. Such a design helps reduce problems associated with pH changes caused by the generation of the electrolytic products H^+ and OH^- . U.S. Patent No. 4,752,285 to Petelenz et al. also describes reactive electrode materials which form insoluble precipitates with a counterion. This approach helps limit the delivery of undesirable metal ions generated by the electrochemistry of the electrode material.

U.S. Patent No. 5,084,008 to Phipps, mentioned briefly above, describes an iontophoretic apparatus which substantially immobilizes electrochemically generated ions by means of a charge selective or size selective membrane between the ion source layer and the drug reservoir. In one embodiment, the '008 patent contemplates an ion exchange resin in the ion source layer. The ion exchange resin is a cation exchange resin if the drug is a cation, and an anion exchange resin if the drug is an anion. The '008 patent also discloses the use of a solid or semisolid gel in the drug reservoir. Nonetheless, the Phipps '008 patent does not provide effective means for efficient

control of ionic migration within the iontophoretic device or the efficiency of drug delivery.

U.S. Patent No. 4,927,408 to Haak et al., discussed briefly above, discloses a variety of selectively permeable membranes to separate the components of the electrolyte and drug reservoirs. Such membranes may be selective on the basis of size (e.g., microporous) and/or charge (e.g., ion exchange or chelation). Optionally, the membrane can be made of a cross-linked hydrogel containing a chelation functionality. The '408 patent does not, however, resolve the problems of ionic control and the associated problem of efficiency of operation.

U.S. Patent No. 4,731,049 to Parsi describes an iontophoretic drug delivery device in which the drug reservoir serves to immobilize the drug by an ion exchange medium or an immobilized ligand affinity medium. In addition, one or more semipermeable membranes may be included in the device, serving as barriers between various compartments or reservoirs. This patent neither teaches nor suggests the use of an ion exchange material in the electrolyte reservoir. Nor does this patent teach or suggest means for controlling electrochemically generated ions, or means for preventing contact of the drug with the current distributing member.

U.S. Patent No. 4,702,732 to Powers et al. describes an iontophoretic device which includes polymeric matrices in both the electrolyte and drug reservoirs. While such polymers may have some degree of porosity, the '732 patent does not teach or suggest the use of such polymers to substantially prevent contact of the drug with the current distributing member or to otherwise assist in control of ionic migration. This patent also fails to recognize any advantages of incorporating an ion capture material in an iontophoretic device. U.S. Patent Nos. 4,383,529 to Webster, 5,135,477 to

Unterecker et al., and 5,203,768 to Haak et al. also disclose the use of gels in the fluid reservoirs of iontophoretic apparatus.

Thus, there has been an unfulfilled need in the field of iontophoresis for an iontophoretic drug delivery device which would eliminate the problems and limitations associated with the prior devices discussed above. Specifically, there has been a need for an iontophoretic drug delivery device which is simple and economical in structure.

There has also been a need for improved control of ion migration in iontophoretic drug delivery devices, to improve current efficiency and to reduce skin irritation and discoloration associated with delivery of undesirable ions, such as electrochemically generated ions, ancillary to delivery of the desired active agent.

Moreover, there has been a need to improve the efficiency and longevity of iontophoretic drug delivery devices when in use, and to produce more effective control of dose rate.

Furthermore, there has been a need to lower the cost of iontophoretic apparatus by significantly reducing the quantities of drug necessary to be incorporated into the apparatus.

SUMMARY OF THE INVENTION

These and other needs are satisfied by the present invention, which provides apparatus for the iontophoretic administration of an ionized or ionizable substance. It has been unexpectedly found that the iontophoretic device of the present invention provides regulation of these similarly charged ions; as used herein regulation is defined as the maintenance of relatively low but substantially constant concentrations of competing ions at the within the iontophoretic device. The essentially constant and low concentration of competing ions in the present invention allows the construction of

relatively small iontophoretic devices having high current efficiency and operating over extended periods of time, as well as enabling these devices to have high dose efficiencies. In the present invention this is accomplished through the actions of the ion regulating means discussed in greater detail below.

In one embodiment, the invention provides a device for the iontophoretic administration of a substance. The device includes:

- (a) a current distributing member;
- (b) an electrolyte reservoir containing an electrolyte, in electrical communication with the current distributing member;
- (c) an ionized substance reservoir containing an ionized or ionizable substance, in ionic communication with the electrolyte reservoir and adapted to be placed in ionic communication with an epithelial surface;
- (d) ion regulating means positioned between the current distributing member and the ionized substance reservoir for capturing electrochemically generated anions and/or cations; and
- (e) the electrolyte reservoir including a polymeric matrix for retaining the ion regulating means.

The polymeric matrix of the electrolyte reservoir substantially inhibits migration of the ionized or ionizable substance into the electrolyte reservoir.

In this embodiment, during application of an electrical potential between the current distributing member and the epithelial surface, migration of electrochemically generated ions between the current distributing member and the ionized substance reservoir is substantially prevented by the action of the ion regulating means, and iontophoretic delivery of the substance from the ionized substance reservoir through said epithelial surface is effected.

In an alternative embodiment, the invention provides a multifunctional iontophoretic reservoir apparatus adapted for use in an electrode device for the iontophoretic administration of a substance. The reservoir apparatus includes:

(a) an electrolyte reservoir, which contains an electrolyte, and which includes a polymeric matrix;

(b) an ionized substance reservoir, which is adapted to contain an ionized or ionizable substance, and which is in ionic communication with the electrolyte reservoir and is adapted to be placed in ionic communication with an epithelial surface;

(c) ion regulating means, which is retained by the polymeric matrix in the electrolyte reservoir, and which substantially prevents migration of electrochemically generated anions and/or cations into the ionized substance reservoir.

The polymeric matrix of the electrolyte reservoir which retains the ion regulating means. The apparatus is also adapted to receive a current distributing member in communication with the electrolyte reservoir.

In this embodiment, the iontophoretic reservoir apparatus is employed with a current distributing member to define an iontophoretic electrode. Due to the capacity of the reservoir to regulate either cations or anions, the reservoir apparatus may be used in either anodal or cathodal administration of ionized substances.

Also, during application of an electrical potential to a current distributing member, through the reservoir apparatus, and across an epithelial surface, migration of electrochemically generated ions between the current distributing member and the ionized substance reservoir is regulated to maintain substantially constant concentration of competing ions in the electrode, which allows for high current efficiency for extended periods of time in small systems, thus enabling high dose efficiency.

In the iontophoretic apparatus of the invention, the current distributing member

may be made of an electrochemically active material, preferably a metal. The electrochemically active material may include a metal such as silver, thallium, copper, zinc, molybdenum, manganese, lead, tin, etc. Alternatively, the electrochemically active electrode may be made of an intercalating compound, such as sodium tungstate or sodium vanadate. In addition, the electrochemically active electrode may be made of an amalgam, such as a mercury amalgam or a cadmium amalgam.

The current distributing member may both a good electron conductor as well as being chemically inert, this is possible for both anode and cathode as discussed in detail in co-pending application entitled: " Low Cost Electrodes For An Iontophoretic Device" by V. Reddy, et al., filed concurrently herewith having U.S. Serial No.: _____, which is incorporated by reference.

In the iontophoretic apparatus of the invention, the ion regulating means may include ion exchange material, a substantially immobilized acid or base, a polyelectrolyte, a chelator, or another such material which is capable of regulating the migration of ions. When the ion regulating means is an ion exchange means, the ion exchange means may include an ion exchange resin, such as cation exchange particles, anion exchange particles, or a mixture of cation and anion exchange particles. Preferably, the ion regulating means includes cation exchange particles and anion exchange particles.

When the ion regulating means includes ion exchange means, the ion exchange means may be a film or membrane having ion exchange functional groups. The functional groups may be cation exchange functional groups, anion exchange functional groups, or may include a mixture of cation and anion exchange functional groups. Preferably, the ion exchange functional groups include cation exchange functional groups and anion exchange functional groups.

When a substantially immobilized acid or base is employed as an ion regulating means, it is preferred that such means should include a substantially immobilized acid, a substantially immobilized base, or a combination of a substantially immobilized acid and a substantially immobilized base. Preferably, such ion regulating means includes substantially immobilized acid and substantially immobilized base. The acid functional groups may be weak acids, strong acids, or combinations thereof. Likewise, the base functional groups may be weak bases, strong bases, or combinations thereof.

If the ion regulating means includes a chelating material, it is preferred that the chelating material include EDTA or a polymeric material having chelating functional groups.

In the iontophoretic apparatus of the invention, it is preferred that the electrolyte reservoir includes a material which permits at least some ion migration. Such materials include gels, such as hydrogels and cross-linked polymers. Alternatively, the ionic migration-permitting material included in the electrolyte reservoir can include a fluid. Preferably, such a fluid includes a density gradient. Preferably, the ion migration-permitting material included in the electrolyte reservoir inhibits the migration of the ionized substance from the ionized substance reservoir into the electrolyte reservoir. More preferably, the material selectively inhibits the migration of substances having molecular weights greater than 3000 daltons. Yet more preferably, the material inhibits the migration of substances having molecular weights in excess of 150 daltons.

The electrolyte reservoir may also include a polymeric electrolyte, preferably a solid or semi-solid material.

The ionized substance reservoir of the iontophoretic apparatus of the invention preferably includes a material which permits at least some ionic migration. It is preferred that this material does not substantially impede migration of the ionized

substance. Such materials include gels, such as hydrogels and cross-linked polymers. Alternatively, the ionic migration permitting material included in the electrolyte reservoir can include a fluid. Preferably, such a fluid includes a density gradient.

In certain embodiments of the iontophoretic apparatus of the invention, the electrolyte reservoir includes a counterion which forms an insoluble salt or precipitate with ions generated from the electrode material as a result of electrochemical forces. For example, when a silver electrode material is employed, it is preferred to include a halide, such as chloride, iodide or bromide, in the electrolyte reservoir as these ions. Alternatively, the electrolyte reservoir can include an ion which forms a soluble salt with a specific electrode material. For example, when a silver electrode material is employed, it may be desirable to include acetate or nitrate as an ion.

The ionized substance reservoir of the iontophoretic apparatus of the invention may further include an electrolyte. In a preferred embodiment, the electrolyte is present in the ionized substance reservoir as a result of the ionized substance itself being present in the form a soluble salt. For example, many ionic drugs are soluble as alkali metal salts or halide salts.

In another embodiment, the electrolyte reservoir of the iontophoretic apparatus of the invention includes ions having a charge of the same sign as ions of the electrode material.

When the electrode of the iontophoretic apparatus of the invention is an anode, it is preferred that the ionized substance have a net positive charge. In such embodiments, it is also preferred that the ion regulating means include cation exchange means or a mixture of cation and anion exchange means. Preferably, the ion regulating means includes cation exchange means and anion exchange means.

When the electrode of the iontophoretic apparatus of the invention is a cathode, it is preferred that the ionized substance have a net negative charge. In such embodiments, it is also preferred that the ion regulating means include anion exchange means or a mixture of anion and cation exchange means. Preferably, the ion regulating means includes cation exchange means and anion exchange means.

The ionized substance included in the ionized substance reservoir of the iontophoretic apparatus of the invention preferably includes a drug, more preferably a peptide.

In a highly preferred embodiment, the iontophoretic apparatus of the invention includes an electrolyte reservoir in which ion exchange particles are substantially immobilized in a gel. Preferably the gel is a cross-linked hydrogel. More preferably, the cross-linked hydrogel substantially excludes substances having molecular weights greater than about 3000 daltons. Still more preferably, the cross-linked hydrogel substantially excludes substances having molecular weights greater than about 150 daltons. In this embodiment, the ion exchange particles include anion exchange particles, cation exchange particles, or a mixture of anion and cation exchange particles. Preferably, the ion exchange particles include anion exchange particles and cation exchange particles.

In the multifunctional iontophoretic reservoir apparatus of the invention, the isolating means preferably substantially inhibits the migration of the ionized substance from the ionized substance reservoir into the electrolyte reservoir. Preferably, the isolating means inhibits the migration of the ionized substance on the basis of molecular weight. Such isolating means include membranes, gels such as hydrogels, particles, or other porous, solid, or semi-solid material. Alternatively, the isolating means inhibits the migration of the ionized substance on the basis of molecular dimension. Such

isolating means include membranes, gels such as hydrogels, particles, or other porous, solid, or semi-solid material. It is preferred that the isolating means substantially restrict or exclude the migration of substances having molecular weights greater than about 3000 daltons. More preferably, the isolating means substantially excludes substances having molecular weights greater than about 150 daltons.

In addition, in the multifunctional iontophoretic reservoir apparatus of the invention, the ion regulating means may comprise a membrane or layer having ion exchange functional groups. Such a membrane may include cation exchange functional groups, anion exchange functional groups, or a mixture of cation and anion exchange functional groups.

For a better understanding of the present invention, reference is made to the following description, taken together with the accompanying figures, the scope of which is pointed out in the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an iontophoretic electrode device of the invention illustrated in transverse section perpendicular to an epithelial surface.

Figure 2 shows another iontophoretic electrode device of the invention illustrated in transverse section perpendicular to an epithelial surface.

Figure 3 shows a multifunctional iontophoretic reservoir apparatus of the invention illustrated in transverse section perpendicular to an epithelial surface.

Figure 4 shows an iontophoretic electrode device of the invention, having an ion exchange membrane and adapted for delivery of a cationic substance, illustrated in transverse section perpendicular to an epithelial surface.

Figure 5 shows an iontophoretic electrode device of the invention, having mixed ion exchange beads and adapted for delivery of a cationic substance, illustrated in transverse section perpendicular to an epithelial surface.

Figure 6 shows an iontophoretic electrode device of the invention, having a semipermeable membrane and adapted for delivery of a cationic substance, illustrated in transverse section perpendicular to an epithelial surface.

Figure 7 shows an iontophoretic electrode device of the invention, having a semipermeable membrane and adapted for delivery of an anionic substance, illustrated in transverse section perpendicular to an epithelial surface.

Figure 8 shows an iontophoretic electrode device of the invention, which has an inert current distributing member and is adapted for delivery of a cationic substance, illustrated in transverse section perpendicular to an epithelial surface.

Figure 9 shows an iontophoretic electrode device of the invention, which has an inert current distributing member and is adapted for delivery of an anionic substance, illustrated in transverse section perpendicular to an epithelial surface.

DETAILED DESCRIPTION OF THE INVENTION

Referring now to Figure 1, an iontophoretic electrode of the invention 10 is shown in transverse section taken perpendicular to an epithelial surface 18. Current distributing member 11 is shown in electrical communication with electrolyte reservoir 12. The electrolyte reservoir 12 includes a polymeric matrix 13, which retains ion exchange resin particles 14 distributed therein. The electrolyte reservoir 12 is shown in ionic communication with the ionized substance reservoir 15, which includes a polymeric matrix 16 in which an ionized or ionizable substance (drug) 17 is distributed.

The ionized substance reservoir 15 is shown in ionic communication with the epithelial surface 18.

With reference to Figure 2, an iontophoretic electrode 20 of the invention is shown in transverse section taken perpendicular to an epithelial surface 28. A current distributing member 21 is shown in electrical communication with the electrolyte reservoir 22. The electrolyte reservoir 22 includes a cross-linked polymeric matrix 23, which includes ion regulating means 24 distributed therein. The electrolyte reservoir 22 is shown in ionic communication with ionized substance reservoir 25, which includes a film in which an ionized or ionizable substance 27 is distributed. The ionized substance reservoir 25 is shown in ionic communication with the epithelial surface 28.

Turning to Figure 3, a multifunctional iontophoretic reservoir apparatus 30 according to the invention is shown in transverse section taken perpendicular to an epithelial surface 38. The reservoir apparatus 30 includes an electrolyte reservoir 32 adapted to be placed in electrical communication with a current distributing member (not shown). The electrical communication between the electrolyte reservoir 32 and the current distributing member (not shown) may be facilitated by the inclusion of a conductive adhesive layer 31, which overlies electrolyte reservoir 32, and is adapted to receive and affix a current distributing member thereon (not shown). The electrolyte reservoir 32 includes a polymeric matrix 33, which retains ion regulating means which for purposes of Figure 3, are in the form of anion and cation exchange resin particles 34 distributed therein. The polymeric matrix 33 is preferably adhesive and is adapted to receive and affix a current distributing member on its upper surface 31. The polymeric matrix 33 is preferably cross-linked. The electrolyte reservoir 32 is shown in ionic communication with the ionized substance reservoir 35, across a membrane 39 which is selective for molecular dimension. The ionized substance reservoir 35 includes a

polymeric matrix 36 in which an ionized or ionizable substance 37 is distributed. The ionized substance reservoir 35 is shown in ionic communication with epithelial surface 38. Figure 3 illustrates an embodiment in which is suitable for delivery of a positively charged drug.

Another preferred embodiment of the present invention is illustrated in Figure 4. In this embodiment, an electrode device of the invention 40 is shown. A current distributing member 41 is shown in electrical communication with the electrolyte reservoir 42. In this embodiment, the ion regulating means function is performed by a mixed function ion exchange membrane 44 as has been described elsewhere herein. The ion exchange membrane permits regulation of ion migration between the electrolyte reservoir 42 and the ionized substance reservoir 45 containing an ionized or ionizable substance 47, which, in this case is illustrated as a cationic drug. The ionized substance reservoir is shown in electrical communication with an epithelial surface 48 such as skin.

The device 40 of this embodiment takes advantage of the fact that roughly half the current flow across the skin is Cl^- upward and half is Na^+ downward when the concentration of these ions is roughly the same on each side of the skin. For this reason, roughly half of the membrane area is cationic exchange, the other half is anionic exchange. This area fraction could be adjusted to more of one type and less of another if a different ratio of transport across skin is desired. Such a situation could occur when, for example, a less than physiological concentration of Na^+Cl^- is desired in the lower reservoir with the drug.

In Figure 4, the electrode device 40 is illustrated as an anode with a positively charged drug (D^+) 47. In this case, 100% of the current from the current distributing member 41 is shown as six (6) Ag^+ ions leaving the metal. Three of these

(since half the membrane is cationic) will interact with the cation portion of the ion exchange membrane and thereby release Na^+ . The other three will interact with the anion portion of the ion exchange membrane 44 by combining with the transported Cl^- to form a AgCl precipitate. Thus, only half of the current passing through the plane of the ion exchange membrane 44 appears in the lower reservoir as Na^+ . The other half of the current across the plane of the ion exchange membrane 44 is Cl^- passing upward. Also note that the drug, D^+ , passes downward through the skin 48, while its counterion, shown as Cl^- , passes upward from the skin through the anion portion of the ion exchange membrane.

In principle, the migration of anions and cations through the plane of the ion exchange membrane can be made identical to the migration of cations and anions through the skin. In this case, the concentration of cations and anions in the lower reservoir stays constant. This is especially true for the chloride counterion, which is neither depleted nor created to excess, and its impact on the current efficiency of drug delivery stays constant.

Figure 4 illustrates only one embodiment of this principle. It is evident that, in this embodiment, the active agent or drug, D^+ (47), is free to exchange across the cation portion of the ion exchange membrane, so it will be diluted over time into the upper reservoir. To prevent such dilution, a size exclusion membrane could be employed, thus creating a third reservoir compartment to contain the drug. Alternatively, the overall volume of the two reservoirs could be made small, so that the drug could equilibrate in both reservoirs, although the drug (D^+) may tend to complex with the anionic sites in the cation portion of the ion exchange membrane.

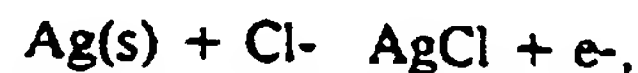
In another alternative, the ion regulating means which is in the form of an ion exchange membrane may itself have size exclusion properties which would prohibit the

active agent from reaching the upper reservoir. It may also be desirable for both cationic and anionic properties to be built into the same membrane. In this concept, as well as in another preferred embodiment which follows, one must also consider the kinetics of the reactions which are occurring. What is really desired is a balance of Na^+ generation and Cl^- removal, and that the sum of these two processes be equal to the Ag^+ generation rate, i.e., equal to the current. The area ratios and the bead concentrations need not be equal, but are adjusted to arrive at the desired result which is ion regulation to achieve equivalence, or fixed proportions of Na^+ generation and Cl^- removal to balance or equilibrate the Na^+ and Cl^- transport across the skin.

A preferred embodiment is shown in Figure 5. In this embodiment, an iontophoretic device 50 includes a current distributing member 51 in electrical communication with the electrolyte reservoir 52. Ion regulating means, shown as mixed anion and cation exchange beads 54, is included in the electrolyte reservoir 52. A differentially permeable membrane 59, such as a size exclusion membrane, separates the electrolyte reservoir 52 from the ionized substance reservoir 55. The ionized substance reservoir 55 is in ionic communication with an epithelial surface 58. During operation of this device, Ag^+ leaves the electrode 51 and has one of two fates: (i) it either binds (with a Cl^-) at the anion exchange bead, or (ii) it exchanges with an Na^+ on the cation exchange bead. The size exclusion membrane 59 permits free migration of both Na^+ and Cl^- , so that, given the proper proportions of the beads, the flux of Na^+ and Cl^- can be driven to any desired values. However, the active agent ion D^+ 57 is sufficiently large that it cannot migrate through the size exclusion membrane enter the upper reservoir 52. This embodiment is particularly useful when the active agent 57 is a peptide.

When the flux of Na^+ and Cl^- have been adjusted so that they are equal to the $(\text{Na}^+ + \text{D}^+)$ and Cl^- transport across the skin 58, the concentration of $\text{Na}^+ \text{Cl}^-$ in the

lower reservoir is made constant. Through the inclusion of ion regulating means in the iontophoretic device, the goals established at the outset have been accomplished. That is, enough fuel (Cl^-) is available (on the anion exchange bead) to handle the fuel requirement. Also, because the electr chemistry is:



and the system conductivity is high overall, (b) pH will be stable and unchanged. In addition, (c) the concentration of the fuel counterion (Na^+) is maintained low and constant through balancing the anion and cation bead concentrations so that Na^+ generation is equal to Na^+ flux into the skin. Moreover, (d) the volume of the active agent reservoir is kept small to provide for high active agent concentration but low active agent mass, which provides for high dose efficiency.

This embodiment is preferred not only for its relative simplicity and ease of bead concentration and hence Na^+ and Cl^- flux rate adjustment, but also for what appears to be a relatively simple manufacturing process. The bead-containing gel can be made ahead of time and provided with an adhesive to which the current distributing member and/or a size exclusion membrane will adhere. Alternatively, the current distributing member could be placed in the gel during the gel manufacturing. As such, this layer need not be "filled" as the active agent reservoir, although hydration of this gel during the packaging phase may be desirable, to activate the adhesive and, if desirable, to supply water to the active agent reservoir during use. The active agent reservoir material is then adhered to the size exclusion membrane, and then filled. The required release liners, backing and sealing materials, and other connectors and packaging are provided as necessary. But being able to fill the design by merely adding fluid to one horizontal surface, rather than having to fill some "hidden" reservoir, is a major advantage of this and other embodiments of the invention.

As has been described elsewhere herein, the ion exchange beads may be

positioned in the electrolyte reservoir, preferably next to the current distribution member to regulate the path length of migration of an electrochemically generated species before bead interaction. Alternative approaches are known for the prevention of migration of such species. For example, U.S. Patent No. 4,927,408 to Haak and U.S. Patent No. 5,084,008 to Phipps describe the use of membranes, both size exclusion (Haak) and ion exchange (Phipps), in electrodes to separate the drug containing space from the electrolytic space. Ideally, in preferred embodiments of the present invention, no such separate membrane would be required.

The drug excluding membrane could be avoided if, for example, the drug ion interacts only minimally with the bead. In general, minimal interaction would be expected since the drug ion in this case is usually a peptide -- much bigger and much less thermodynamically active than small elemental ions. Still, the degree of interaction would have to be measured and beads selected to keep the interaction to a minimum. Alternatively, the drug excluding membrane can be dispensed with if the dilution of the drug into the bead binder (assuming that the solvent for the drug is water and the beads are found in a gel) does not dramatically alter the concentration of the drug in the reservoir. This clearly depends upon the exchange capacity of the beads.

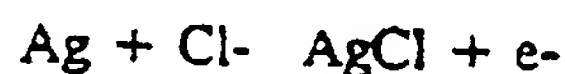
It is also possible to get very low competing fuel counterion concentrations in a small volume, yet be able to maintain the desired electrochemistries for extended periods of time and have only Na⁺ and Cl⁻ ions involved (plus, of course, the drug ion).

This most preferred embodiment is illustrated in Figure 6. This embodiment includes current distributing member 61 in electrical communication with the electrolyte reservoir 62. The electrolyte reservoir includes a polymeric matrix 63 which retains cation exchange beads 64. The electrolyte reservoir is in ionic communication with the ionized substance reservoir 65, which contains an ionized or ionizable substance 67.

The ionized substance reservoir 65 is, as is described elsewhere herein, in ionic communication with an epithelial surface 68. The electrode device 60 also includes a semipermeable membrane 69 which restricts movement of substances based on molecular weight. Thus, keeping the ionizable or ionized substance 67 from migrating from the ionized substance reservoir 65 to the electrolyte reservoir 62 and eliminates dilution of the ionized substance 67 in the electrolyte.

In this embodiment, in which an anodal system 60 is employed to deliver a cationic drug D^+ 67, the drug D^+ 67 has a molecular weight greater than the molecular weight cut-off (MWCO) of the size selective membrane 69. The drug D^+ is therefore restricted to the drug reservoir 65. In formulation with the drug is a low concentration of electrolyte, for example, <0.01 M NaCl. The same concentration of this electrolyte is maintained in the electrolyte reservoir 62 to impart conductivity to the overall system.

The following ionic transport occurs at the skin 68 in this anodal system as shown in Figure 6. The drug D^+ ions 67 and Na^+ ions traverse the skin 68 from the drug reservoir 65. Na^+ ions also are driven away from the skin surface 68. Cl^- ions pass from the skin 68 into the drug reservoir 65 and move toward the anode 61. With a silver current distributing member 61 in the presence of Cl^- , the well-known reaction



will take place. However, in this reservoir system, because not enough Cl^- comes across the skin to maintain the initial Cl^- concentration, there is not enough Cl^- present to maintain the Ag/AgCl electrochemistry. As the Cl^- concentration drops, the voltage at the water/metal interface rises. When the Cl^- reaches a critically low concentration, the electrochemistry switches to:



As this reaction continues, the Ag^+ migrates to the skin, giving rise to the adverse

effect known as "tattooing" or skin discoloration. In the past, tattooing has been avoided by providing enough Cl^- in the electrolyte reservoir to maintain the Ag/AgCl reaction.

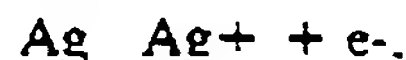
Conventional wisdom says that, if you need more Cl^- in a small volume, and you want to use an ion exchange bead, the Cl form of an anion exchange bead would be used. This teaching is found in WO92/04938 to Chien et al. and U.S. Patent No. 4,973,303 to Johnson et al. However, our experiments have shown that the conventional wisdom is wrong because, in an ion exchange bead, one ion must be exchanged for another, and both ions must be of the same charge. However, the only ions available to exchange with the Cl^- ion are D^+ and Cl^- . Moreover, since 100% of the current at the metal/water interface is e^- from Cl^- , and since only about half of the current at the skin or between the reservoirs is anions toward the anode -- the remainder being D^+ and Na^+ moving toward the cathode -- very quickly Cl^- is depleted and Ag^+ begins to enter into solution. While there is ample Cl present in the beads, in this system there is no way to exchange it off the beads.

The present invention solves this problem through the ion regulating means in this case through the use of cation exchange beads in the electrolyte reservoir. Use of cation exchange beads according to the present invention causes the following sequence of events to occur:

Since at the start of iontophoresis a sufficient concentration of Cl^- is present, the first reaction to occur is:



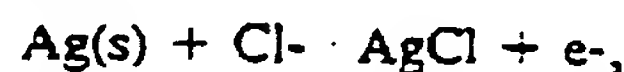
As stated above, the Cl^- concentration drops because more Cl^- is consumed than is replaced by transport across the skin. At some point the second reaction:



would take over as iontophoresis continues. Eventually, the Ag^+ would migrate to the skin and result in tattooing. However, because the cation exchange bead containing Na^+ is present, Ag^+ is exchanged for Na^+ at the bead. When the reaction at the anode is:



followed by Ag^+ exchanging for Na^+ at the cation exchange bead, the result is a net increase in the electrolyte concentration in the system due to Na^+ coming from the beads and Cl^- coming from the skin. As the Cl^- concentration rises, the electrochemistry switches back to:



which tends to reduce the electrolyte concentration. As iontophoresis continues, the result is an equilibrium between the two electrochemical reactions. Most importantly, Na^+ , Cl^- and D^+ are transported at the skin, with Na^+ at a low concentration in the reservoir, but continually being replenished at this low concentration by the exchange of Ag^+ for Na^+ at the beads. Thus, the present invention achieves regulation of similarly charged ions by maintaining substantially constant concentrations of competing ions in the electrode, thereby allowing high current efficiency for extended periods of time.

The above anodal system (as shown in Figure 6) is not limited to silver current distributing members. Any metal for which the reaction to an insoluble salt has a lower potential than the reaction to the metallic ion in solution should work. Other suitable metals may include, but are not limited to, thallium, copper, and iron.

For modification to the system for delivery of an anionic drug (D^-), such as insulin above its isoelectric point, the following analogous situation can be exploited. In this case, an intercalation compound, amalgam, or other compound that can take sodium ions out of solution below the reduction potential of water can be used as a cathode

material. An electrode configuration such as that shown in Figure 7 could be used.

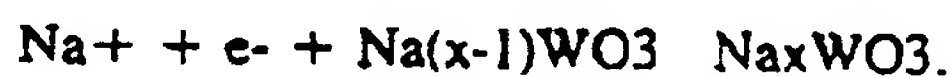
Figure 7 shows a preferred embodiment which is adapted for the delivery of an anionic drug. A cathodal device 70 is shown, including a current distributing member 71 in electrical communication with the electrolyte reservoir 72. The electrolyte reservoir includes a polymeric matrix 73 which supports and retains ion regulating means shown as ion exchange beads 74. A semipermeable membrane 79 separates the electrolyte reservoir from the ionized substance reservoir 75, but permits migration of substances having molecular weights below a certain cut-off. The ionized substance reservoir 75 includes an ionized or ionizable substance, D^- , 77, shown as an anionic drug, and is in ionic communication with an epithelial surface 78.

Note that Figures 6 and 7 both show an electrolyte reservoir and a drug reservoir separated by a size exclusion membrane. The purpose of this membrane is to provide a small reservoir for the drug to give high dose efficiency and to keep the beads from interacting with the drug. There is a good likelihood that drug adsorption on the bead which would occur if the membrane were absent.

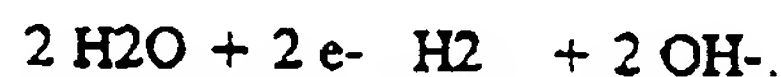
However, it should be noted that this embodiment would still operate without the membrane. Such an embodiment would be useful in situations in which dose efficiency is not as important or when the drug does not interact with the beads. Alternatively, the absence of a membrane is less critical when formulation additives, such as surfactants, are employed to prevent adsorption of the drug on the beads. Normally such additives are themselves inert to the iontophoretic process. Other methods may be used to prevent the drug from interacting with the beads, such as ion exchange membranes, gels having different degrees of cross-linking, or gels having different degrees of hydrophobicity. Any means may be employed which at least substantially eliminates bead/drug interaction and/or provides a smaller drug reservoir to give high drug

concentration with a small loaded dose to provide high dose efficiency.

For cathodal delivery of an anionic drug using a system such as that shown in Figure 7, an operation, analogous to that given for the anodal delivery of a cationic drug (Figure 6), can be described. For an intercalation cathode such as sodium tungstate the reaction at the cathode is:



This reaction occurs at a cathode/water potential which is lower than that required to reduce water. Water is therefore not involved in this reaction. Since the Na^+ is consumed in this reaction at a rate higher than it is replenished by transport across the skin, the concentration of Na^+ falls during the course of iontophoresis. In order to deliver the current, again the electrochemistry will switch; in this case, to the reduction of water at a voltage of -0.84 V. The reaction is:



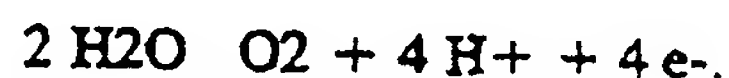
Hydrogen gas is evolved and hydroxide ions are generated into solution. If the anion exchange beads weren't present the pH of the solution would rise and skin damage would occur. However, because the anion exchange beads are present, as the OH^- concentration starts to rise, Cl^- ions will be competed off the beads by the OH^- ions, creating a molecule of water at the bead as well and driving the Cl^- ions into solution. Again we have an equilibrium reaction. In this case, there is an effective equilibrium between the intercalation of Na^+ , which is preferred by nature and reduces the Na^+ concentration, and the reduction of water, which increases the Na^+ concentration. Thus, the electrochemistry continues, as long as the intercalation compound can intercalate, with only a very low concentration of Na^+ and Cl^- present to compete with delivery of the drug.

The same kind of equilibrium reaction can be obtained using inert electrodes and mixed anionic and cation exchange beads as shown in Figures 8 and 9.

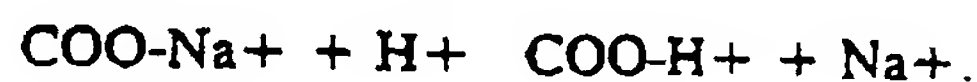
Figure 8 shows an iontophoretic device of the invention which includes a chemically inert anodal current distributing member 81. The current distributing member is in electrical communication with the electrolyte reservoir 82, which contains a polymeric matrix 83 supporting an ion regulating means in the form of a cation exchange beads 84. A differentially permeable membrane 89 separates the electrolyte reservoir 82 and the ionized substance reservoir 85, while permitting migration of substances having low molecular weights. The ionized substance reservoir contains an ionized or ionizable substance, which in this case is a cationic drug 87. Ionic communication is permitted between the ionized substance reservoir 85 and the epithelial surface 88.

Figure 9, by contrast, shows an iontophoretic device of the invention which includes a chemically inert cathodal current distributing member 91. The current distributing member is in electrical communication with the electrolyte reservoir 92, which contains a polymeric matrix 93 supporting an ion regulating means in the form of an anion exchange beads 94. A differentially permeable membrane 99 separates the electrolyte reservoir 92 and the ionized substance reservoir 95, while permitting migration of substances having low molecular weights. The ionized substance reservoir contains an ionized or ionizable substance, which in this case is an anionic drug 97. Ionic communication is permitted between the ionized substance reservoir 95 and the epithelial surface 98.

In the case of an inert anode for the delivery of a cationic drug, the electrochemistry at the electrode involves the electrolysis of water:



At the cation exchange bead, assuming carboxylic acid substituents, hydrogen ions are captured in exchange for Na^+ ions:

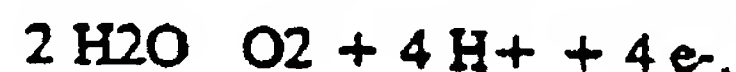


At the anion exchange bead, assuming amino substituents, H_3O^+ ions and Cl^- ions combine on the bead:



At first, there is a small amount of Na^+Cl^- in the electrolyte reservoir, but very little H^+ . The only reactant for the beads is Cl^- , so as iontophoresis begins only the anionic beads interact. But the Cl^- concentration in the electrolyte reservoir falls as time passes since more Cl^- is consumed than replenished through the skin. At some Cl^- concentration, there will not be enough Cl^- to keep the anionic reaction going, so the cationic reaction starts to play an increasing role. But the cationic reaction cannot become the only reaction because that would mean that the Cl^- concentration would rise. Hence, an equilibrium reaction is maintained, providing a low overall Cl^- concentration between the anionic and cationic beads.

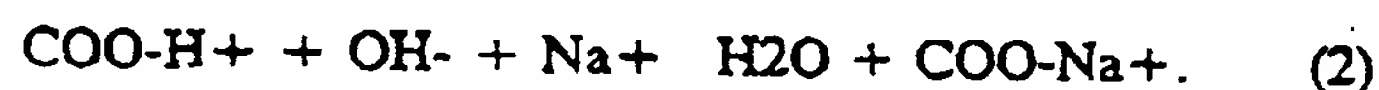
For an inert cathodal system of delivery of an anionic drug, a similar situation exists. Again, at the electrode, the electrolysis of water occurs:



At the cationic bead, assuming amino substituents, hydroxyl ions are captured and exchanged for Cl^- ions, which go into solution as follows:



At the anionic bead, assuming carboxylic acid substituents, hydroxyl ions react with the bead and with Na^+ ions to pull the Na^+ ions out of solution as follows:



The resultant equilibrium is partially dependent upon the pH of the system. If the pH of the reservoir is above the pK_a of the COOH substituents, i.e., $\text{pK}_a \approx 3$, the COOH will be easily deprotonated by the OH^- . In this situation, the reaction at the anionic bead will be preferred. Thus, Na^+ ions will be removed from solution. To

balance this, either another Na^+ ion must enter the electrolyte reservoir or a Cl^- ion must leave. As a result, the NaCl concentration of the electrolyte reservoir will fall with time. At some point, there won't be enough Na^+ to keep this reaction going. At that time, OH^- will start to accumulate, thereby raising the pH, until the complementary reaction starts at the cationic bead. Both reactions will proceed in equilibrium, as an increase in NaCl will drive Reaction 2 which reduces NaCl concentration, while a decrease in NaCl will drive Reaction 1 which increases NaCl . Given the foregoing description of preferred embodiments, a more thorough discussion of the elements of the iontophoretic devices of the invention is now presented.

A. The Current Distributing Member

The iontophoretic electrode of the invention includes a current distributing member which conveys electrical current into the iontophoretic reservoirs for the delivery of an ionized substance. The current distributing member is constructed of any of a large variety of electrically conductive materials, including both inert and sacrificial materials.

Inert conductive materials are those electrically conductive materials which, when employed in the iontophoretic devices of the invention, do not themselves undergo or participate in electrochemical reactions. Thus, an inert material distributes current without being eroded or depleted due to the formation of ions of the material. Such electrodes generally operate at potentials which cause the electrolysis of water to generate hydroxyl (OH^-) ions at the cathode and hydronium (H_3O^+) ions at the anode. These ions may then be said to "electrochemically generated" ions. Inert conductive materials typically include, for example, stainless steel, platinum, gold, and carbon or graphite.

Alternatively, the current distributing member may be constructed from a

sacrificial conductive material. A material may be considered sacrificial if, when employed as an electrode in an iontophoretic device of the invention, the material is eroded or depleted due to its oxidation or reduction. Such erosion or depletion would occur if a material's electrode potential is within the range of potentials employed in the iontophoretic device. In this situation, the current distributing member would not cause electrolysis of water, but would itself be oxidized or reduced.

Typically, for anodes, a sacrificial material would include an oxidizable metal such as silver, zinc, copper, etc. In contrast to the hydroxyl and hydronium ions electrochemically generated via an inert material, the ions electrochemically generated via a sacrificial material would include metal cations resulting from oxidation of the metal. Metal/metal salt anodes may also be employed. In such cases, the metal would oxidize to metal ions, which would then be precipitated as an insoluble salt.

For cathodes, the current distributing member may be constructed from any electrically conductive material. For example, the cathodic current distributing member may be constructed from a metal/metal salt material. A preferred cathodic material is a silver/silver halide material. In such embodiments, a metal halide salt is preferably employed as the electrolyte. In this case, the device would electrochemically generate halide ions from the electrode as the metal is reduced. Also, accompanying silver ions would be reduced to silver metal and would deposit (plate) onto the electrode. In other embodiments, the cathode material may be an intercalation material, an amalgam, or other material which can take electrolyte cations such as sodium out of solution, below the reduction potential of water. In addition, other materials may be used which permit the plating out of a metal from the appropriate electrolyte solution. Thus, metals such as silver, copper, zinc, and nickel, and other materials, such as carbon, may be employed when an appropriate metal salt such as silver nitrate or zinc sulfate is in solution in the electrolyte reservoir. While such materials may develop increased

resistivity as a metal plates out during use, they are not eroded or depleted during use as cathodic current distributing members. They are therefore not strictly "sacrificial" in this context.

Additional types of materials useful as current distributing members according to the invention are disclosed in detail in a co-pending application entitled Low-Cost Iontophoretic Device, by Reddy et al., Serial No. _____, filed concurrently herewith, the disclosure of which is incorporated by reference herein.

The current distributing member may take any form known in the art, such as the form of a plate, foil layer, screen, wire, or dispersion of conductive particles embedded in a conductive matrix.

B. The Electrolyte Reservoir

1. Electrolytes

In the iontophoretic devices of the invention, an electrolyte reservoir is arranged in electrical communication with a current distributing member. Typically, electrical communication requires that electrons from the current distributing member are exchanged with ions in the electrolyte reservoir upon the application of electrical current. Such electrical communication is preferably not impeded to any excessive degree by any intervening material(s) used in the construction of the iontophoretic device. In other words, the resistivity of the interface is preferably low.

The electrolyte reservoir comprises at least one electrolyte, i.e., an ionic or ionizable component which can act to conduct current toward or away from the current distributing member. Typically, the electrolyte comprises one or more mobile ions, the selection of which is dependent upon the desired application. Examples of suitable electrolytes include aqueous solutions of salts. A preferred electrolyte is an aqueous

solution of NaCl, having a concentration of less than 1 mole/liter ($< 1\text{ M}$), more preferably at about physiological concentration. Other electrolytes include salts of physiological ions including, but not limited to, potassium, (K^+), calcium (Ca^{2+}), chloride (Cl^-), and phosphate (PO_4^{3-}). The salt and its concentration may be selected as desired for particular applications. Other species may be selected by the skilled artisan for inclusion in the electrolyte reservoir. Such other reservoir species include, without limitation, surfactants (e.g., non-ionic, cationic, or anionic), buffers, ionic excipients, osmolarity adjusters (e.g., polyethylene glycols, sugars), ionic antibiotics, penetration enhancers (e.g., alkanols), stabilizers, enzyme inhibitors, preservatives, thickening agents (e.g., acrylic acids, cellulosic resins, clays, polyoxyethylenes), and the like.

Alternatively, the electrolyte may comprise a material which is itself relatively immobile in the absence of an electric field, but which acts to deliver mobile ions in the presence of an electric field. In the latter case, the electrolyte may more properly be termed an "ion source." Examples of ion sources according to the invention include polyelectrolytes, ion exchange membranes and resins, non-ionic buffers which become ionic upon pH change, and other known ion sources.

The electrolyte reservoir may include one or more ions that form an insoluble complex with an electrochemically generated ion. For example, as a means of sequestering metal ions produced by oxidation at an anode, the electrolyte reservoir may contain an ion that forms an insoluble salt with the metal ions. This approach is exemplified in apparatus in which the current distributing member is silver and a halide (e.g., chloride, bromide, iodide) ion is included in the electrolyte reservoir.

Alternatively, the electrolyte reservoir may contain counterions that form a soluble salt with an electrochemically generated ion. For example, in an apparatus

employing a silver anodal current distributing member, a suitable counterion might be acetate or nitrate. Such counterions are useful when other means are provided for sequestering electrochemically generated ions.

Thus, the electrolyte reservoir can provide at least one ion of the same charge as the electrochemically generated ion, to permit current to be conducted, and at least one oppositely charged ion.

B. The Electrolyte Reservoir

2. Polymeric Matrix

The electrolyte reservoir further includes a matrix in which the electrolyte is distributed. The matrix may have a physical consistency which is liquid, semi-liquid, semi-solid, or solid, depending upon the desired application. In the preferred embodiments, the electrolyte reservoir includes a polymeric matrix, which imparts a solid or semi-solid consistency to the electrolyte reservoir. In any event, the matrix of the electrolyte reservoir should not excessively impede the migration of current toward or away from the current distributing member. Preferably, the matrix should have minimized effect on the mobile current-carrying components, i.e., the electrolyte ions. Thus, in the case in which the electrolyte includes a small mobile ion, the mobility of the ion should not be impeded significantly.

Alternatively, if a particular ion is desired to be rendered mobile while another, perhaps larger, ion is to be rendered immobile, the electrolyte matrix may be a polymeric material having a defined microstructure. In such cases, the polymeric material is selected to impede the mobility of the larger ion based on its physical dimensions, while the smaller ion is relatively less impeded.

In its broadest definition, the preferred material suitable for use as a polymeric

matrix is a porous, hydrophilic composition which supports a confluent aqueous phase and has a high initial resistance to electric current. The polymeric matrix should not conduct electrical current. Rather, electrical current should only be conducted by the ions in the confluent aqueous phase. The polymeric matrix must be porous, having tiny holes or apertures through which small molecules may pass. The porosity of the matrix material is not particularly critical unless it is desired that the matrix material operate as the means for excluding the agent from the electrolyte reservoir. "Porosity" is a quantity defined herein as the total volumetric percentage of void space within the matrix. Similarly, the pore size of the matrix material is not critical unless the matrix material itself is employed to exclude the agent from the electrolyte reservoir. "Pore size" is a quantity defined herein as the dimension of the passageways or apertures within the matrix. In application, the average diameter of the pores must be at least large enough to permit mobility of certain of the ions in the electrolyte reservoir.

The polymeric matrix forming the reservoir should be physically and chemically stable under the intended storage and use conditions. The matrix material should not be subject to degradation or decomposition over a wide range of conditions including moderate heat and cold, as well as electric fields of varying strength. The matrix material should also be stable over prolonged periods of time. Similarly, materials that react with the agent to be delivered are also generally not suitable. The matrix material should also be non-toxic and biocompatible (nonirritating) with the subject's tissues. Preferably, the polymer can be fabricated with ease and be configurable using conventional molding or casting techniques to meet predetermined dimensions and/or geometric configurations.

Various classes of polymers are believed to be useful as polymeric matrices in the electrolyte reservoirs of the present invention, including: acrylamide polymers, acrylic acid, and methacrylic acid polymers, alkyds, butadienes, carboxylic products,

cellulose ethers and other cellulose products, epoxy products, ethylene oxide polymers and related products, fluoropolymers, formaldehyde products, gelatin and gelatin products, inorganic products, natural gums, polyamides and polyamids, polyesters, polyethylene glycol derivatives, polyethylamine and related products, polysiloxanes and related products, polyurethane products, polyvinyl alcohol and related products, polyvinyl pyrrolidone and related products, and similar polymeric compositions which do not easily fit into one of the aforementioned classes. Preferred materials useful as polymeric matrices in the electrolyte reservoir include, without limitation, polyvinyl pyrrolidone (available from ISP Chemicals in Wayne, New Jersey, and from BASF), polyoxyethylenes (e.g., Polyox, available from Union Carbide), acrylates (e.g., Carbopol, available from BF Goodrich), polyvinyl alcohols (e.g., Elvanol, available from DuPont, Wilmington, Delaware) and hydroxypropyl, hydroxyethyl, and hydroxymethyl cellulose (available from Aqualon, Wilmington, Delaware).

The porosity and pore size of polymeric materials conventionally used in the art are rather high. Such materials have a molecular weight cut-off of about 3,000 daltons or greater. Such materials are generally useful according to the invention if they are employed with a more restrictive membrane between the electrolyte reservoir and the agent reservoir. It has been observed, however, that, in contrast to the prior art, a cross-linked hydrogel material may preferably be employed as the matrix material in the apparatus of the invention without the requirement for an excluding membrane. Such cross-linked hydrogels may be formulated as desired to yield a molecular weight cut-off preferably excluding substances larger than about 1000 daltons. Most preferably the cross-linked hydrogel excludes substances larger than about 100 daltons.

The increased selectivity of such cross-linked polymers allows small ionic species

to migrate freely through the matrix under the influence of an electric field, while drug molecules are impeded or excluded due to their size. For example, smaller agents such as peptides may effectively be excluded by means of a cross-linked hydrogel, but would pass through the pores of a polymer having a molecular weight cut-off which is even fractionally too large. Such small peptide compounds include, for example, luteinizing hormone releasing hormone (LHRH), somatostatin, vasopressin, cholecystokinin, and natural and synthetic analogs thereof.

As a result, it is an advantage of the iontophoretic apparatus of the invention that a cross-linked hydrogel matrix can perform multiple functions. In particular, the cross-linked hydrogel can serve to retain an ion regulating means such as an ion exchange resin. The cross-linked hydrogel can also act as a size selective medium to substantially inhibit movement of the agent into the electrolyte reservoir. In addition, since cross-linked hydrogels have a high water content, they can act as a reservoir of water, to replenish water lost from the ionized substance reservoir during iontophoresis. The use of such crosslinked hydrogels substantially simplifies the structure of the iontophoretic apparatus of the invention, resulting in an advantageous lowering costs of manufacture and operation.

The polymeric matrix of the electrolyte reservoir may also contain any of a wide variety of functional chemical components which are chosen to interact with the electrochemically generated ions. Such components include polyelectrolytes, polymers with weak acid functional groups such as carboxylic acids, polymers with weak base functional groups such as amines, polymers with chelating groups, or sulfonated resins and other strong cation exchange resins.

C. The Ionized Substance (Drug) Reservoir

The reservoir structure of the iontophoretic apparatus of the invention further includes an ionized substance reservoir. This reservoir includes the ionized or ionizable substance(s) to be iontophoretically delivered. Among other properties, the ionized substance reservoir must be in ionic communication with the electrolyte reservoir. Thus, at least one ion must be capable of traversing the boundary between the two reservoirs. In preferred embodiments, movement of the substance from the ionized substance reservoir into the electrolyte reservoir is substantially prevented. Thus, in most embodiments at least one other ion must be capable of traversing the boundary between the electrolyte reservoir and the ionized substance reservoir.

In addition, the ionized substance reservoir must be in ionic communication with an epithelial surface. At a minimum, this requires that the substance desired to be iontophoretically delivered should not be substantially impeded from traversing the boundary between the ionized substance reservoir and the epithelial surface. In certain embodiments, it may be desirable that another ion or ions be substantially capable of traversing the boundary between the ionized substance reservoir and the epithelial surface. This is preferred in cases in which the current across the epithelium is desired to be carried, at least in part, by ions other than the agent being delivered. For example, in the delivery of a cationic drug, it may be desirable that part of the current arise from the movement of physiological anions from the epithelial surface in the iontophoretic apparatus.

The construction of the ionized substance reservoir must be consistent with the requirements described above for ionic communication with the electrolyte reservoir and with the epithelial surface. Accordingly, the structure of the ionized substance reservoir would vary, depending upon the desired application. The ionized substance reservoir may include a liquid, semi-liquid, semi-solid, or solid material. With a

flexible material, the ionized substance reservoir preferably further comprises means for at least substantially inhibiting the flow of the contents out of the reservoir. In such situations, the flow of the contents is desirably minimized when the device is in storage. For example, a membrane may be deployed to surround the contents of the ionized substance reservoir. In certain situations the flow of the contents of the reservoir may be minimized while in storage, but increased in use. For example, a surrounding membrane may increase in porosity, permeability, or conductivity upon the application of an electric field across the membrane. Examples of such membranes are disclosed in U.S. Patent Nos. 5,080,546; 5,169,382; and 5,232,438, the disclosures of which are incorporated by reference herein.

In preferred embodiments, the ionized substance reservoir is constructed to retain its physical integrity and to inherently resist migration and loss of the ionized substance. Such embodiments include those in which the ionized substance reservoir includes a solid or semi-solid material such as a gel or other polymeric material. In an especially preferred embodiment, the ionized substance reservoir includes a polymeric film in which the substance to be iontophoretically delivered is dispersed. The mobility of the substance to be delivered is substantially increased by the application of the electric field, permitting effective delivery across the target epithelial surface. Such a film need not contain any significant amount of hydrating material. In preferred embodiments, a cross-linked hydrogel in the electrolyte reservoir, because it inherently contains significant amounts of water, can serve as a water reservoir during iontophoresis.

D. The Ion Regulating Means

The iontophoretic apparatus of the invention further includes ion regulating means. The ion regulating means may include any material that substantially controls the migration of electrochemically generated ions between a current distributing member and the ionized substance reservoir. In an iontophoretic electrode of the

invention, the ion regulating means is typically located between the current distributing member and the ionized substance reservoir, to maintain substantially constant concentrations of competing ions in the iontophoretic electrode device. In a multifunctional iontophoretic reservoir apparatus of the invention, which typically lacks but is adapted to receive a current distributing member, the ion regulating means is located so as to effectively isolate the drug to be delivered from any electrochemically generated ions. For example, the ion regulating means may be located in the electrolyte reservoir, preferably near the site at which the reservoir apparatus would contact the current distributing member. By way of example, and not limitation, the ion regulating means may be located within the polymeric matrix of the electrolyte reservoir. Alternatively, the ion regulating means may include a membrane or film between the electrolyte reservoir and the ionized substance reservoir.

The ion regulating means is used to control the ability of electrochemically generated ions in the electrolyte chamber to reach the skin of the patient. When using sacrificial materials, such as silver, as the anode, it is important to prevent migration of the metal ions, and so to prevent the metals ions from contacting the skin and ultimately tattooing the skin of the patient. Tattooing also occurs at the cathode when metal ions migrate from the electrolyte reservoir by countercurrent diffusion onto the skin and become deposited therein. Additionally, the ion regulating means prevents the metal ions present in the electrolyte from passively diffusing into the drug compartment, i.e., the compartment which will eventually contact the skin, during storage of the iontophoretic device. Tattooing may also occur at the anode of the iontophoretic device. Metal ions generated at the anode by the electrochemical process should be prevented from entering the ionized substance reservoir and being driven by the iontophoretic device into the skin of the patient.

The ion regulating means useful according to the invention may take any of a

large variety of physical and/or chemical forms. Broadly speaking, the ion regulating means either is disposed in the electrolyte reservoir or occurs in a membrane or layer positioned between the ionized substance reservoir and the electrolyte reservoir.

In embodiments in which the ion regulating means is disposed within the electrolyte reservoir, the ion regulating means may be in the form of an ion exchange resin, a polyelectrolyte, a chelating agent, or a buffer. Typically, such materials are substantially immobilized in the polymeric matrix of the electrolyte reservoir. For example, the ion regulating means may comprise either or both of a substantially immobilized weak acid and a substantially immobilized weak base. It is also to be understood that some ions in the electrolyte reservoir may be employed to form an insoluble salt with the electrochemically generated ions, thus acting as ion regulating means.

In embodiments in which the ion regulating means is positioned at the interface between the electrolyte reservoir and the ionized substance reservoir, the ion regulating means typically is in the form of a membrane, film, or layer possessing ion exchange, polyelectrolyte, chelation and/or buffer properties.

In preferred embodiments, the ion regulating means includes an ion exchange material. Depending upon the desired application, the ion exchange material is selected to exhibit anion exchange, cation exchange, or mixed anion/cation exchange properties.

In one preferred embodiment, the ion exchange material includes ion exchange resin distributed in the polymeric matrix of the electrolyte reservoir. In this embodiment, the spatial distribution of the ion exchange resin is desirably retained by the polymeric matrix. As a result, the ion exchange resin may be distributed in a discrete layer within the matrix of the electrolyte reservoir. The matrix will thereby substantially prevent migration of the resin due to physical and/or chemical forces

acting within the iontophoretic device. For example, a layer of ion exchange resin is preferably disposed adjacent or proximate to the current distributing member to facilitate sequestration of electrochemically generated ions. Thus, for an anode, a layer of cation exchange resin particles may be disposed at or near the anodic current distributing member. Conversely, for a cathode, a layer of anion exchange resin particles may be disposed at or near the cathodic current distributing member. Alternatively, in the case of a multifunctional iontophoretic reservoir apparatus according to the invention, a mixed ion exchange layer, including both cation and anion exchange resins, may be positioned within the electrolyte reservoir. Thus, the multifunctional reservoir apparatus of the invention may be employed with either a cathodic or an anodic current distributing member, and would be capable of exchanging any electrochemically generated ions, whether anions or cations.

In another preferred embodiment, the ion exchange material includes a membrane or film at the interface between the electrolyte reservoir and the ionized substance reservoir. In this embodiment, the film or membrane may be made of an ion exchange material, or may be made of a polymeric material in which an ion exchange resin is dispersed. For embodiments in which the ion exchange material includes mixed anion/cation exchange material in a membrane or film, the membrane or film is preferably mosaic in structure. Such a mosaic membrane possesses discrete microscopic or macroscopic regions which exchange ions of only a single charge. Thus, the membrane may include regions which exhibit only anion exchange function and other regions which exhibit only cation exchange function. The regions may be arranged or may occur in random relation to one another. It is believed that a distribution of anion and cation exchange functions in separate overlying layers would render a membrane or film effectively non-conductive. Accordingly, a polymeric layer in which mixed anion and cation exchange resin beads or particles are dispersed would

provide desirable qualities according to the invention.

E. Isolating Means

The isolating means of the present invention is designed to substantially inhibit the migration of ionized or ionizable substances (agents) from the ionized substance reservoir into the electrolyte reservoir. This inhibition of ionized or ionizable substances is accomplished on the basis of molecular weight. Such isolating means may include a membrane or film which is selective based on molecular dimension. Such materials include semipermeable or differentially permeable membranes such as cellulose-based dialysis membranes or polycarbonate microporous membranes. In certain embodiments, a suitable membrane would possess both size-selective and charge-selective properties. This type of membrane can effectively exclude the agent from the electrolyte reservoir on the basis of size, and control the migration of other ions on the basis of ionic charge.

The selectively permeable membrane material can be chosen to suit the particular needs of the system and will depend upon the composition of the electrolyte reservoir, i.e., electrochemical reactants and products, the transference of current out of the reservoir, and the desired selectivity to transport of particular types of charged and uncharged species. A microporous polymer such as is known in the art, can be utilized if the electrolyte reservoir and agent reservoir components can be separated on the basis of molecular size. Therefore, a selectively permeable membrane comprised of a microporous polymer can be used to substantially exclude entry into the electrolyte reservoir of agents having greater than a predetermined molecular weight. Suitable materials include, without limitation, polycarbonates, i.e., linear polyesters of carbonic acids in which carbonate groups recur in the polymer chain by phosgenation of a dihydroxy aromatic such as bisphenol A, polyvinylchlorides, polyamides such as polyhexamethylene adipamide and other such polyamides commonly known as "nylon".

modacrylic copolymers such as those formed of polyvinylchloride and acrylonitrile, and styrene-acrylic acid copolymers, polysulfones such as those characterized by diphenylene sulfone groups in the linear chain thereof, halogenated polymers such as polyvinylidene fluoride and polyvinylfluoride, polychloroethers and thermoplastic polyethers, acetal polymers such as polyformaldehyde, acrylic resins such as polyacrylonitrile, polymethyl methacrylate and poly n-butyl methacrylate, polyurethanes, polyimides, polybenzimidazoles, polyvinyl acetate, aromatic and aliphatic polyethers, cellulose esters such as cellulose triacetate, cellulose, collodion, epoxy resins, olefins such as polyethylene and polypropylene, porous rubber, cross-linked poly(ethylene oxide), cross-linked polyvinylpyrrolidone, cross-linked poly(vinyl alcohol); derivatives of polystyrene such as poly(sodium styrenesulfonate) and polyvinylbenzyl trimethylammonium chloride, poly(hydroxyethyl methacrylate), poly(isobutyl vinyl ether), polyisoprenes, polyalkenes, ethylene vinyl acetate copolymers, polyurethanes, polyethylene oxides, polyox, polyox blended with polyacrylic acids, cellulose derivatives such as hydroxypropyl cellulose, pectin, starch, guar gum, locust bean gum, and the like, along with blends thereof. This list is merely exemplary of the materials suited for use as membranes in this invention. A particularly preferred size exclusion membrane is the Diaflo YC05 ultrafiltration membrane sold by the Amicon division of W.R. Grace and Co., Danvers, Massachusetts.

An ion-exchange membrane such as is known in the art, can be utilized as the selectively permeable membrane, if the electrolyte reservoir and drug reservoir components can be separated on the basis of their charge characteristics. Therefore, a selectively permeable membrane composed of an ion exchange membrane could be used to inhibit transport of species having a given ionic charge. Suitable ion exchange membranes include anionic and cationic membranes sold under the trademark Raipore .

by The Electrosynthesis Co., East Amherst, N.Y. These can provide ion-exchange capacities within the range of 0.8-1.5 meq/g and resistance within the range of 0.2-17 ohm cm² (measured in 0.6N KCl). A particularly preferred anion exchange membrane is sold as ESC 7001 by PALL, East Hills, New York.

The ion-exchange membrane may be used to control the movement of ionic species by only allowing species of a specific ionic charge to pass through, and may be either of the same or opposite charge that the agent or drug to be delivered. For example, for a positive drug, an anion-exchange membrane will inhibit the drug from moving into the electrolyte reservoir and will inhibit positive ions in the electrolyte reservoir from moving into the agent or drug reservoir where they would compete with the drug for charge transference. However, if the object is to prevent a negatively charged species in the electrolyte reservoir from entering the drug reservoir and causing precipitation of the drug, it would be advantageous to use a cation-exchange membrane in order to prevent this movement.

An ion-exchange membrane can also be used to specifically bind an interfering species and/or replace it with another. For example, a chelating membrane will effectively remove all metals, especially divalent ones, from solution. Also, a sodium loaded ion exchange film may be used to replace hydrogen ions. Note that it is important that the membrane have enough capacity to last for the duration of the treatment. For an electrotransport system operating for a 24 hour period at a current of 0.1 mA, the ion-exchange capacity needed will be approximately 9×10^{-5} equivalents. Typical commercially available ion exchange membranes are 0.1-0.5 mm thick and are on the order of 10^{-3} eq/cm³. These factors should be taken into consideration when selecting a suitable membrane.

The selectively permeable membrane may also be a hydrogel, preferably at least

partially cross-linked, and loaded with a chelating agent to trap the metal ions produced during the discharge of the electrode. This is particularly desirable when the metal ions may damage the skin or body surface. Use of a hydrogel/chelating agent membrane is therefore ionically selective, entrapping the metal ions while allowing passage of the counterions. The hydrogel can be any state of the art material including, without limitation, polyvinyl alcohol, polyacrylamide, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, polyacrylic acid, polyvinyl pyrrolidone, hydroxyethyl methacrylate, albumin, gelatin, and cellulose. Suitable chelating agents include, without limitation, ethylenediamine tetraacetic acid (EDTA) and ionexchange resins such as Chelex 100. Also suitable for use as a material for a selectively permeable membrane in the apparatus of the invention is a cross-linked polyhemoglobin, such as is described in U.S. Patent No. 4,001,200. Cross-linked polyhemoglobin by itself can perform the functions of both the hydrogel and the chelating agent.

F. Protective Backing

The iontophoretic apparatus of the invention may also include a suitable backing film positioned on top of the electrolyte reservoir. The backing film provides protection against contamination and damage to the current distributing member, if present, and the electrolyte reservoir of the apparatus.

G. Release Liner

The iontophoretic apparatus of the invention optionally includes a release liner which may be fixed to the underside of the ionized substance reservoir by an adhesive. The release liner protects the surface of the ionized substance reservoir which contacts the epithelial surface from contamination and damage when the device is not in use. When the device is ready for use, the release liner may be peeled off to expose the epithelial contacting surface of the ionized substance reservoir for application of the

device to a patient.

H. Indifferent Electrode

Iontophoretic devices require at least two electrodes to provide a potential to drive drug ions into the skin of a patient. Both electrodes are disposed to be in intimate electrical contact with the skin thereby completing the electrochemical circuit formed by the anode pad and cathode pad of the iontophoretic device. The electrode pads may be further defined as an active electrode from which an ionic drug is delivered into the body. An indifferent or ground electrode serves to complete the electrochemical circuit. In some cases, depending upon the electrode materials, a battery or other current source is coupled to the electrodes to provide the electrical force to drive the drug ions into the body. A galvanic couple may be employed such as is described in concurrently filed and co-pending United States application entitled Low-Cost Iontophoretic Device, by Reddy et al., Serial No. _____.

I. The Ionizable Substance (Drug) for Iontophoretic Delivery

An ionic drug can be delivered from either the anode, the cathode, or both simultaneously. For example, if the ionic substance to be driven into the body is positively charged, then the positive electrode or anode will be the active electrode and the negative electrode or cathode will serve to complete the electrochemical circuit. Alternatively, if the ionic substance to be delivered is negatively charged, then the negative electrode will be the active electrode and the positive electrode will be the indifferent electrode. Although the preferred embodiments of the present invention are directed to ionic drugs driven by the anode of the iontophoretic device, it is to be understood that a similar configuration can be used to drive negatively charged ionic substances from the cathode without departing from the spirit of the invention.

It is believed that this invention has utility in connection with the delivery of active ingredients within the broad class normally delivered through epithelial surfaces and membranes, including skin, mucosa, and nails. Virtually any active ingredient capable of assuming an ionized form is contemplated as useful in the present invention, and the active ingredient must be at least partially in ionized form at the time of iontophoretic delivery. As used herein, the expressions "agent", "drug", "active ingredient", "ionized substance", and "ionizable substance" are used interchangeably, and are intended to have their broadest interpretation as any therapeutically active substance which is delivered to a living organism to produce a desired, usually beneficial, effect. In general, this includes therapeutic agents in all of the major therapeutic areas including, but not limited to: anti-infectives such as antibiotics and antiviral agents, analgesics and analgesic combinations, anesthetics, anorexics, antiarthritics, antiasthmatic agents, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheal agents, antihistamines, antiinflammatory agents, antimigraine preparations, antimotion sickness preparations, antinauseants, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics including gastrointestinal and urinary, anticholinergics, sympathomimetics, xanthine derivatives, cardiovascular preparations including calcium channel blockers, beta blockers, antiarrhythmics, and antihypertensives, diuretics, vasodilators including general, coronary, peripheral and cerebral, central nervous system stimulants, cough and cold preparations, decongestants, diagnostics, hormones, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetics, proteins, peptides, psychostimulants, sedatives, tranquilizers, contraceptives, hormone replacement therapies, and anti-obesity drugs. Preferred therapeutic agents include analgesics, anesthetics, antiarthritics, antimigraine preparations, antinauseants, hormones, parasympathomimetics, peptides, and contraceptives. It is preferable to use the most water soluble form of the drug or agent to be delivered, which in most instances is the

salt form of said drug or agent.

It may be desirable to provide the solution of active ingredient with a buffer. The ion of the buffer of like charge to the drug ion should have low ionic mobility. The limiting ionic mobility of this ion is preferably no greater than 1×10^{-4} cm²/volt-sec. The buffer can include large multiply-charged ions or weak anion exchange resin or weak cation exchange resin. The buffer ions should have a smaller charge to mass ratio than the active ingredient. The pK of the weak anion exchange resin should be in the range of about 4 to 7, preferably about 6. Desirably, the anion exchange resin is useful at a pH of about 5-14. One example of such a resin is Amberlite IRP-695 resin sold by Rohm & Haas Company, of Philadelphia, Pennsylvania. The pK of the weak cation exchange resin should be in the range of about 6 to 10, preferably about 9. Desirably, the cation exchange resin is useful at pH of about 5-14. One example of such a resin is Amberlite CG-50 resin also sold by Rohm & Haas Company.

While the present invention has been described in connection with iontophoresis, it should be appreciated that it may be used in connection with other principles of active introduction, i.e., motive forces. Accordingly, the invention is understood to be operative in connection with electrophoresis, which includes the movement of particles in an electric field toward one or the other electric pole (anode or cathode), and electroosmosis, which includes the transport of uncharged compounds due to the bulk migration of water induced by an electric field. Also it should be appreciated that the patient or subject may include humans as well as animals.

EXAMPLES

Example 1

An iontophoretic patch was constructed in which a microporous membrane was

employed as the drug reservoir, an agarose gel containing a cation exchange resin was employed as the electrolyte reservoir, and a membrane was employed to separate the drug reservoir from the electrolyte reservoir.

As constructed, the electrode was silver mesh. The drug reservoir was a μ PES-4f film from AKZO. The separator was a YMI ultrafiltration membrane (1000 m.w. cut-off) from Amicon. The upper, electrolyte reservoir included a 3% gel of agarose (SeaKem Gold, FMC) containing 0.3 g/ml Amberlite IRP69 cation exchange resin (Rohm & Haas). The electrolyte reservoir also contained 10 mM NaCl and 10 mM MES buffer at pH 6. The patch had a contact area of 0.5 cm², and a fill-volume of 12 μ L/cm².

The patch was loaded with 6 μ L of a solution of a calcitonin at a concentration of 6 mg/mL in 10 mM MES (pH 6) with 0.01% Tween80 (a surfactant) and 10 mM NaCl.

Example 2

In this example, an iontophoretic patch was constructed according to the invention. In this case a cross-linked hydrogel was employed in the electrolyte reservoir which limited migration of solutes on the basis of molecular dimension.

As constructed, the electrode for the patch was a silver mesh. The drug reservoir was a μ PES-4f film from AKZO. The electrolyte reservoir included 10% PVA containing 10% Amberlite IRP69 cation exchange resin. The electrolyte reservoir contained 10 mM NaCl, with 60-70% water content. The patch had a contact area of 0.5 cm², and a fill-volume of 12 μ L/cm².

The patch was loaded with 6 μ L of a solution of a calcitonin at a concentration of 6 mg/mL in 10 mM MES (pH 6) with 0.01% Tween80 (a surfactant) and 10 mM NaCl.

Example 3

The comparative performance of patches constructed as described in Examples 1 and 2 was evaluated according to a method accepted in the art as follows:

The patches were tested for iontophoretic delivery of Calcitonin in swine. Current was applied (0.8 mA) for 4 hours, followed by 4 hours clearance. The plasma drug concentration as a function of time was recorded and plotted, thereby representing the pharmacokinetic profile of drug delivery. The area under the curve (AUC) for patch administration was calibrated against previously known AUCs for intravenous (IV) and intramuscular (IM) administration, and the comparisons are shown in Table 1, below.

TABLE 1
PLASMA AUC COMPARISON OF PVA/IRP69
AND AGAROSE/IRP69 WITH YMI SEPARATORS

Description (all w/ YMI IM)	Run	Load (units)	AUC (units vs. IV)	AUC (units vs.
Agarose/ IRP69	1	216	29.5	78
	2	216	29.0	73
PVA/ IRP69	1	216	34.0	87
	2	216	32.5	83
Average \pm s.e.		216	31 \pm 1	80 \pm 3

The patches with PVA/IRP69 upper reservoirs provided slightly higher delivery of a calcitonin than the agarose/IRP69 patches. However, for practical purposes, there is no difference in a calcitonin delivery when agarose is replaced by PVA in a membrane-separated patch. Thus, the baseline configuration with a YMI separator delivers approximately 31 units of a calcitonin vs. the available dose by IV injection, or vs. 80 units by the available dose from IM injection, from an initial load of 216 units at 0.8 mA in 1 cm².

Example 4

In experiments, the iontophoretic system of the invention has demonstrated substantially improved capacity for ionic regulation. In a reservoir with 0.01 M NaCl, using the in vitro flow system, with 100 μ L of electrolyte reservoir volume containing Na⁺ form of cation exchange beads, iontophoresis was carried out for 24 hours at 200 μ A/cm² with no tattooing. By contrast, with only 10⁻⁶ moles of Cl⁻, at 200 μ A total current (1 cm² area) a system without cation exchange beads would run for only eight (8) minutes before exhaustion of the chloride ion source. This calculation assumes the following relationship:

$$\frac{\text{Faraday constant} \times \text{equivalent charge} \times \text{Amount of Cl}^-}{\text{Current}} = \text{Duration.}$$

In this case, the equation is:

$$\frac{96,500 \text{ coul/eq} \times 1 \text{ eq/mole} \times 10^{-6} \text{ mole}}{200 \times 10^{-6} \text{ coul/sec} \times 60 \text{ sec/min}} = 8 \text{ minutes.}$$

Upon disassembling the reservoir, inspection showed no chloriding of the silver, while the AgCl precipitate was mixed in with the beads. This would be expected, since once the Ag(s) \rightarrow Ag⁺ + e⁻ reaction starts, there is no requirement for the competing reaction Ag⁺ + Cl⁻ \rightarrow AgCl(s) + e⁻ to take place at the electrode. The first reaction,

producing AgCl as a precipitate, will occur where the Cl⁻ concentration is high enough. Based on the above analysis, such precipitation will occur at the bead layer. Thus the bead layer is preferably placed farther from the skin, and closer to the anode, to avoid extraneous and undesirable reactions at the skin.

Theoretical Analysis of the Relationship
Between Drug Dilution and Dose Efficiency

The following calculation, as an example, can determine the degree of drug dilution and its effect on dose efficiency. In the following calculation, the geometry shown in Figure 1 is assumed. In this concept, there is a fluid retaining means, such as Porex, to hold the drug in aqueous solution in drug reservoir 20. It is preferred that the ion exchange beads have capacities in the range of 5-10 meq/g. If the current density is 200 $\mu\text{A}/\text{cm}^2$, then the number of meq needed per cm^2 (assuming valence = 1) is:

$$\frac{200 \mu\text{A} \times 3600 \text{ sec/hr} \times 24 \text{ hr}}{96,500 \text{ coulomb/mole}} = 0.18 \text{ meq/cm}^2$$

If the bead has a capacity of 5 meq/g, 36 mg of beads/ cm^2 is required. The beads have a density of about 3 g/ cm^3 , and, thus, take up a volume of roughly 12 μL . Therefore, it is feasible to have the silver mesh and the beads in a layer less than 0.5 mm thick. A reasonable geometry would be:

silver	12 μL	(125 μm thick);
beads	12 μL	(125 μm thick);
gel	26 μL	(260 μm thick, projected).

Now assume that the drug reservoir 20 is 0.5 mm thick, and is 50% void (Porex). Thus, there is 25 $\mu\text{L}/\text{cm}^2$ of the drug formulation. If the concentration is 15 mg/mL uniformly through both layers, there is 50 $\mu\text{L}/\text{cm}^2$ which calculates to 750 $\mu\text{g}/\text{cm}^2$. At 200 μA , we have seen fluxes ranging from 50 ng/min (DBS Porex with 100 mM saline) to 150 ng/min (20 mM saline with 0.5% Triton X-100 in hydrophobic Porex). At 50 ng/min, the delivered daily dose is 72 $\mu\text{g}/\text{cm}^2$, which calculates to a dose efficiency of

9.6%. At 150 ng/cm², the delivered daily dose is 216 µg/cm², and the dose efficiency would be 28.8%.

These dose efficiencies are clearly in the useful range. Modest adjustment of the volumes of the various layers could have a beneficial effect of putting the dose efficiency at a desired value. Clearly, however, no membrane is needed to get high dose efficiency with the reservoir system of the invention.

The daily dose and dose rate of any therapeutic agent depends on the potency of the drug or substance to be delivered and the effective therapeutic window. Generally, by way of example, useful dose efficiency is greater than about 5%, preferably greater than about 20%, and most preferably greater than about 33%. More specifically, a useful dose range of dose efficiency would be greater than about 10% for peptides, with preferred dose efficiencies above about 20%. For small molecules (i.e., <500 daltons), the useful dose efficiency usually above about 20%, and the preferred levels are above about 40%. These dose efficiencies are presented as exemplary, and are not intended to limit the invention.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that other changes and modifications may be made thereto without departing from the spirit of the invention, and we intend to claim all such changes and modifications as falling within the true scope of the invention.

WHAT IS CLAIMED IS:

1. A device for the iontophoretic administration of a substance, comprising:
 - (a) a current distributing member;
 - (b) an electrolyte reservoir containing an electrolyte, in electrical communication with the current distributing member;
 - (c) an ionized substance reservoir containing an ionized or ionizable substance, in ionic communication with the electrolyte reservoir and adapted to be placed in ionic communication with an epithelial surface;
 - (d) ion regulating means positioned between the current distributing member and the ionized substance reservoir for capturing electrochemically generated anions and/or cations; and
 - (e) the electrolyte reservoir including a polymeric matrix for retaining said ion regulating means;wherein, during application of an electrical potential between the current distributing member and the epithelial surface; migration of electrochemically generated ions between the current distributing member and the ionized substance reservoir is substantially prevented, and iontophoretic delivery of the substance from the ionized substance reservoir through the epithelial surface is effected.
2. The iontophoretic device of Claim 1, wherein said ion regulating means comprises ion exchange means.
3. The iontophoretic device of Claim 2, wherein said ion exchange means comprises cation exchange resin particles, anion exchange resin particles, or a mixture thereof.
4. The iontophoretic device of Claim 2, wherein said ion exchange means comprises cation exchange means and anion exchange means.
5. The iontophoretic device of Claim 2, wherein said ion exchange means comprises a film having ion exchange functional groups.
6. The iontophoretic device of Claim 5, wherein said ion exchange functional groups comprises cation exchange functional groups, anion exchange functional groups, or a combination thereof.
7. The iontophoretic device of Claim 5, wherein said ion exchange functional groups comprises cation exchange means and anion exchange means.
8. The iontophoretic device of Claim 1, wherein said ion regulating means comprises a substantially immobilized acid, a substantially immobilized base, or a combination thereof.

9. The iontophoretic device of Claim 8, wherein said ion regulating means comprises a substantially immobilized base and a substantially immobilized acid.

10. The iontophoretic device of Claim 8, wherein said ion regulating means comprises a substantially immobilized weak acid, a substantially immobilized weak base, or a combination thereof.

11. The iontophoretic device of Claim 8, wherein said ion regulating means comprises a substantially immobilized weak base and a substantially immobilized weak acid.

12. The iontophoretic device of Claim 8, wherein said ion regulating means comprises a substantially immobilized strong acid, a substantially immobilized strong base, or a combination thereof.

13. The iontophoretic device of Claim 8, wherein said ion regulating means comprises a substantially immobilized strong base and a substantially immobilized strong acid.

14. The iontophoretic device of Claim 1, wherein said ion regulating means comprises a polyelectrolyte.

15. The iontophoretic device of Claim 1, wherein said ion regulating means comprises a chelating material.

16. The iontophoretic device of Claim 15, wherein said chelating material comprises EDTA.

17. The iontophoretic device of Claim 15, wherein said chelating material comprises a polymeric material having chelating functional groups.

18. The iontophoretic device of Claim 1, wherein said electrolyte reservoir comprises a material which permits ion migration.

19. The iontophoretic device of Claim 18, wherein said ion migration-permitting material comprises a gel.

20. The iontophoretic device of Claim 19, wherein said gel comprises a hydrogel or a cross-linked polymer.

21. The iontophoretic device of Claim 19, wherein said ion migration-permitting material selectively inhibits the migration of substances having molecular weights greater than about 150 daltons.

22. The iontophoretic device of Claim 18, wherein said electrolyte reservoir comprises a polymeric electrolyte.
23. The iontophoretic device of Claim 22, wherein said polymeric electrolyte is a solid.
24. The iontophoretic device of Claim 1, wherein said electrolyte reservoir comprises a gel and wherein said ion regulating means comprises ion exchange particles substantially immobilized in said gel.
25. The iontophoretic device of Claim 24, wherein said gel is a hydrogel.
26. The iontophoretic device of Claim 24, wherein said gel selectively inhibits the migration of substances having molecular weights greater than about 150 daltons.
27. The iontophoretic device of Claim 24, wherein said ion exchange particles comprise anion exchange particles, cation exchange particles, or a mixture thereof.
28. The iontophoretic device of Claim 24, wherein said ion exchange particles comprise anion exchange particles and cation exchange particles.
29. The iontophoretic device of Claim 24, wherein said ionized substance comprises a drug.
30. The iontophoretic device of Claim 29, wherein said drug is a peptide.
31. A multifunctional iontophoretic reservoir apparatus adapted for use in an electrode device for the iontophoretic administration of a substance, the reservoir apparatus comprising:
- (a) an electrolyte reservoir containing an electrolyte;
 - (b) an ionized substance reservoir containing an ionized or ionizable substance, in ionic communication with the electrolyte reservoir and adapted to be placed in ionic communication with an epithelial surface;
 - (c) ion regulating means positioned to substantially prevent entry of electrochemically generated anions and/or cations into said ionized substance reservoir;
 - (d) isolating means positioned to prevent contact of said ionized substance with said current distributing member; and
 - (e) said electrolyte reservoir including a polymeric matrix for retaining said ion regulating means;
- wherein, during application of an electrical potential between said current distributing member and said epithelial surface; migration of electrochemically generated ions between the current distributing member and the ionized substance

reservoir is substantially prevented, and iontophoretic delivery of said substance from said ionized substance reservoir through said epithelial surface is effected.

32. The iontophoretic reservoir apparatus of Claim 31, wherein said isolating means substantially inhibits the migration of the ionized substance from the ionized substance reservoir into the electrolyte reservoir.

33. The iontophoretic reservoir apparatus of Claim 32, wherein said isolating means inhibits the migration of the ionized substance on the basis of molecular weight.

34. The iontophoretic reservoir apparatus of Claim 33, wherein said molecular weight isolating means comprises a membrane, a gel, or particles.

35. The iontophoretic reservoir apparatus of Claim 34, wherein said gel selectively inhibits the migration of substances having molecular weights greater than about 150 daltons.

36. The iontophoretic reservoir apparatus of Claim 31, wherein said ion regulating means comprises ion exchange means.

37. The iontophoretic reservoir apparatus of Claim 36, wherein said ion exchange means comprises ion exchange resin particles.

38. The iontophoretic reservoir apparatus of Claim 37, wherein said ion exchange resin particles comprise cation exchange resin particles, anion exchange resin particles, or a mixture of cation exchange resin particles and anion exchange resin particles.

39. The iontophoretic reservoir apparatus of Claim 38, wherein said ion exchange means comprises cation exchange resin particles and anion exchange particles.

40. The iontophoretic reservoir apparatus of Claim 36, wherein said ion exchange means comprises a film having ion exchange functional groups.

41. The iontophoretic reservoir apparatus of Claim 40, wherein said ion exchange functional groups include cation exchange functional groups, anion exchange functional groups, or a mixture thereof.

42. The iontophoretic reservoir apparatus of Claim 40, wherein said ion exchange functional groups include cation exchange functional groups and anion exchange functional groups.

43. The iontophoretic reservoir apparatus of Claim 31, wherein said ion

regulating means comprises a substantially immobilized acid, a substantially immobilized base, or a mixture thereof.

44. The iontophoretic reservoir apparatus of Claim 31, wherein said ion regulating means comprises a substantially immobilized acid and a substantially immobilized base.

45. The iontophoretic reservoir apparatus of Claim 44, wherein said ion regulating means comprises a substantially immobilized weak acid, a substantially immobilized weak base or a combination thereof.

46. The iontophoretic reservoir apparatus of Claim 44, wherein said ion regulating means comprises a substantially immobilized weak acid and a substantially immobilized weak base.

47. The iontophoretic reservoir apparatus of Claim 44, wherein said ion regulating means comprises a substantially immobilized strong acid, a substantially immobilized strong base, or a mixture thereof.

48. The iontophoretic reservoir apparatus of Claim 44, wherein said ion regulating means comprises a substantially immobilized strong acid and a substantially immobilized strong base.

49. The iontophoretic reservoir apparatus of Claim 31, wherein said ion regulating means comprises a polyelectrolyte.

50. The iontophoretic reservoir apparatus of Claim 31, wherein said ion regulating means comprises a chelating material.

51. The iontophoretic reservoir apparatus of Claim 50, wherein said chelating material comprises EDTA.

52. The iontophoretic reservoir apparatus of Claim 50, wherein said chelating material comprises a polymeric material having chelating functional groups.

53. The iontophoretic reservoir apparatus of Claim 31, wherein said electrolyte reservoir comprises a material which permits ionic migration.

54. The iontophoretic reservoir apparatus of Claim 53, wherein said ionic migration permitting material comprises a gel.

55. The iontophoretic reservoir apparatus of Claim 54, wherein said gel substantially inhibits migration of the ionized substance from the ionized substance reservoir into the electrolyte reservoir.

56. The iontophoretic reservoir apparatus of Claim 55, wherein said gel selectively inhibits the migration of substances having molecular weights greater than about 150 daltons.

57. The iontophoretic reservoir apparatus of Claim 53, wherein said electrolyte reservoir comprises a polymeric electrolyte.

58. The iontophoretic reservoir apparatus of Claim 57, wherein said polymeric electrolyte is a solid.

59. The iontophoretic reservoir apparatus of Claim 31, wherein said electrolyte reservoir comprises a gel and wherein said ion regulating means comprises ion exchange particles substantially immobilized in said gel.

60. The iontophoretic reservoir apparatus of Claim 59, wherein said gel is a cross-linked hydrogel.

61. The iontophoretic reservoir apparatus of Claim 60, wherein said gel is a cross-linked hydrogel which substantially excludes substances having a molecular weight of greater than about 150 daltons.

62. The iontophoretic reservoir apparatus of Claim 60, wherein said ion exchange particles comprise cation exchange particles or a mixture of cation exchange particles and anion exchange particles.

FIG-1

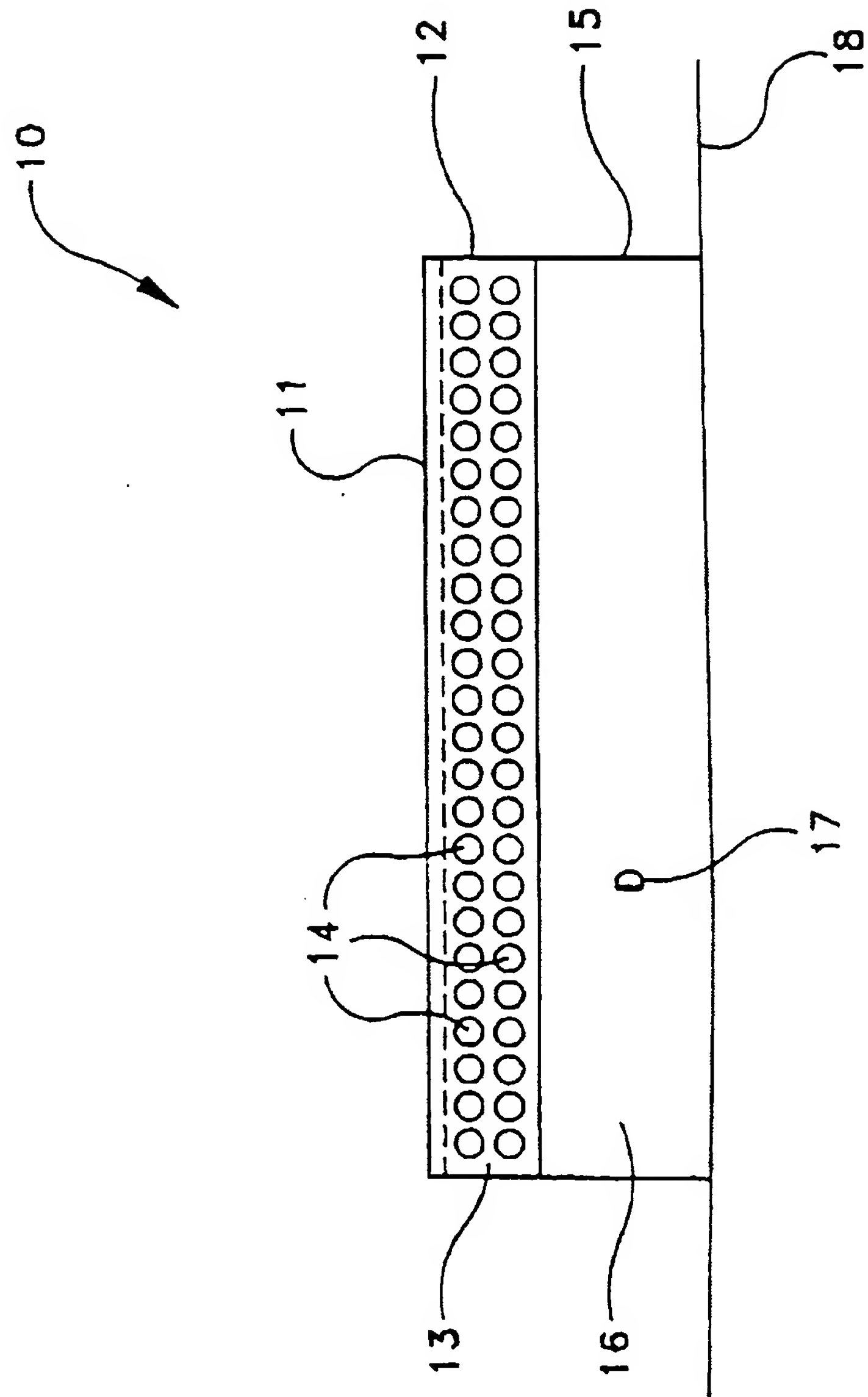


FIG-2

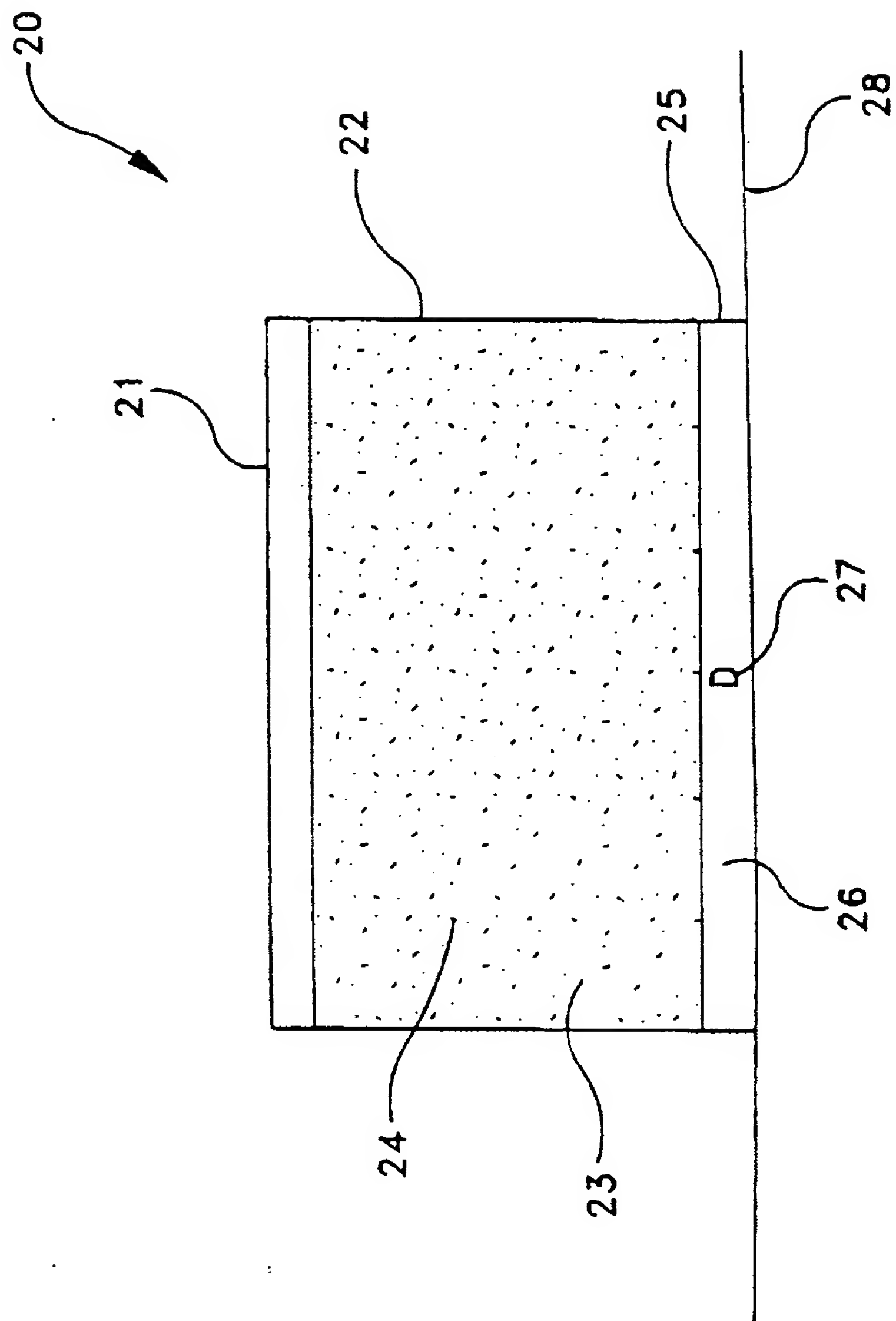
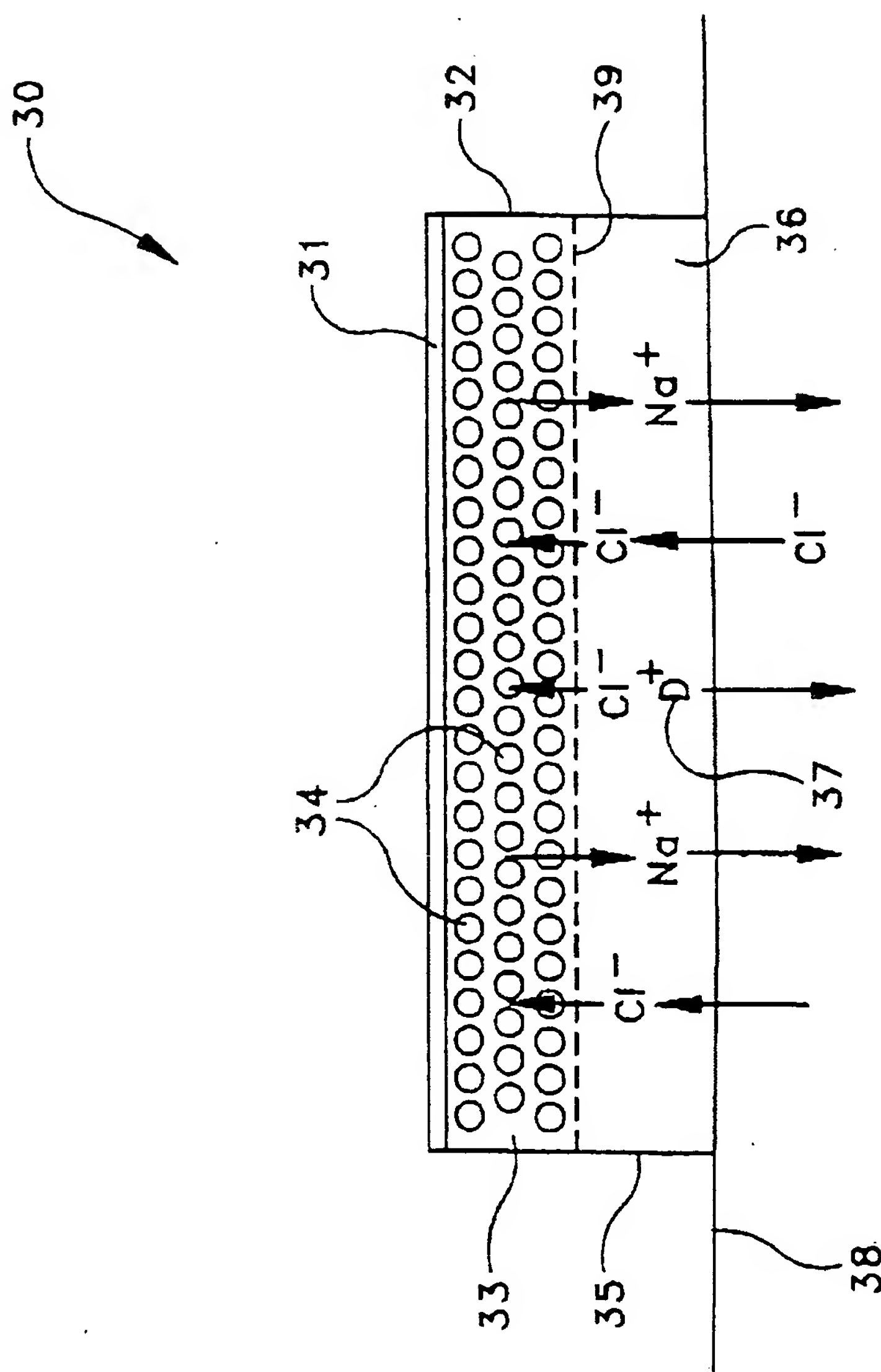


FIG-3



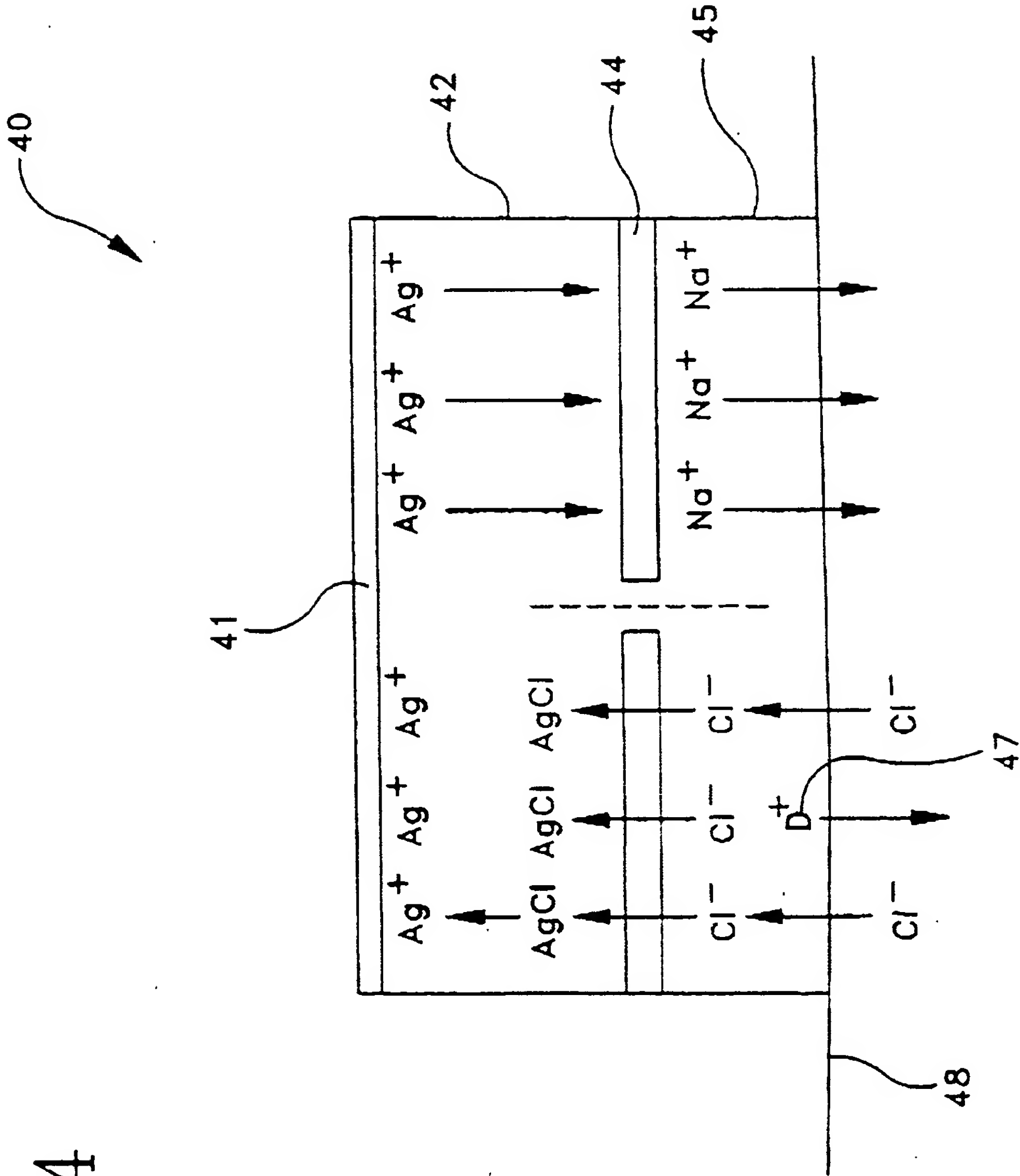
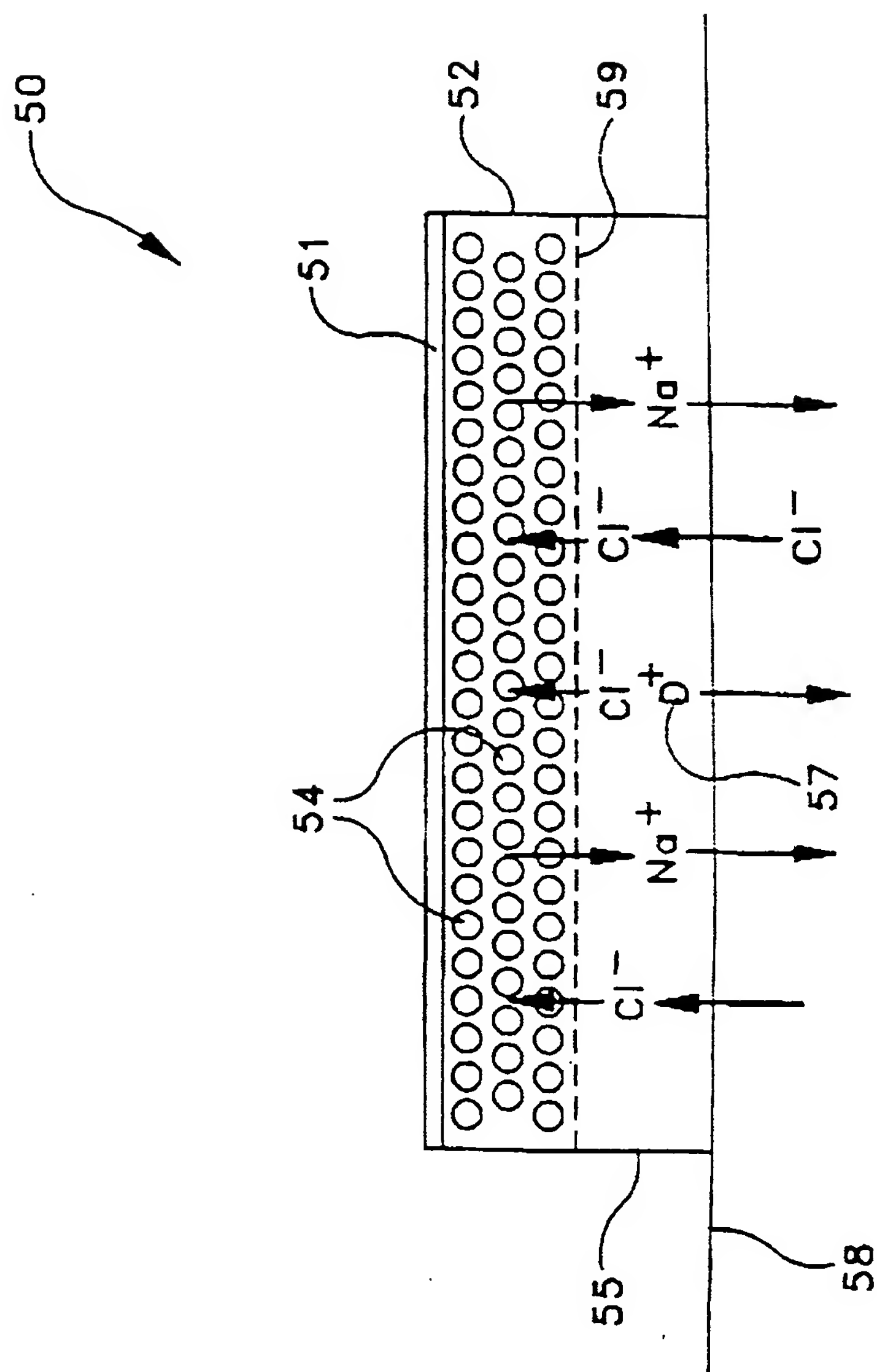


FIG-4

FIG-5



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FIG-6

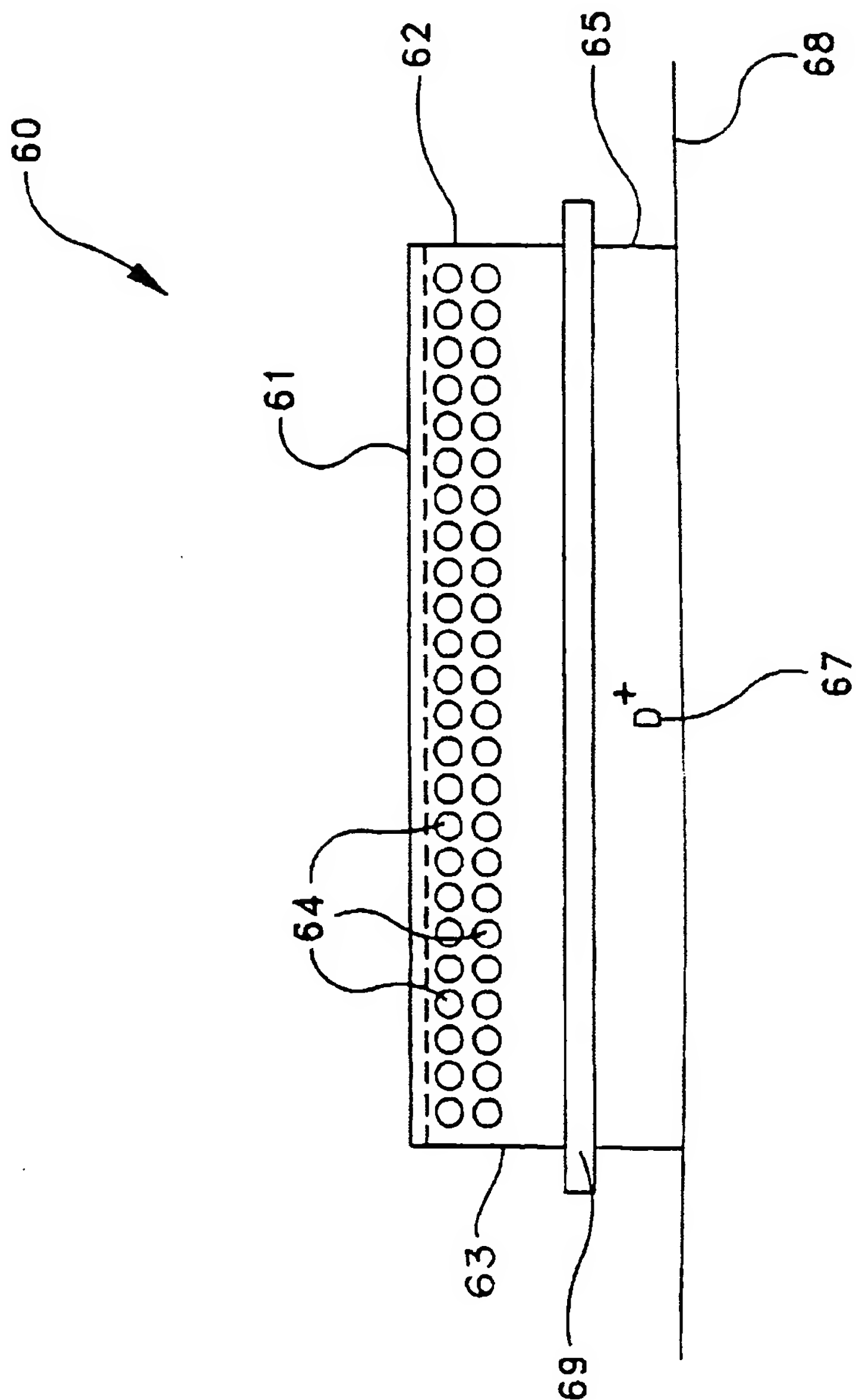


FIG-7

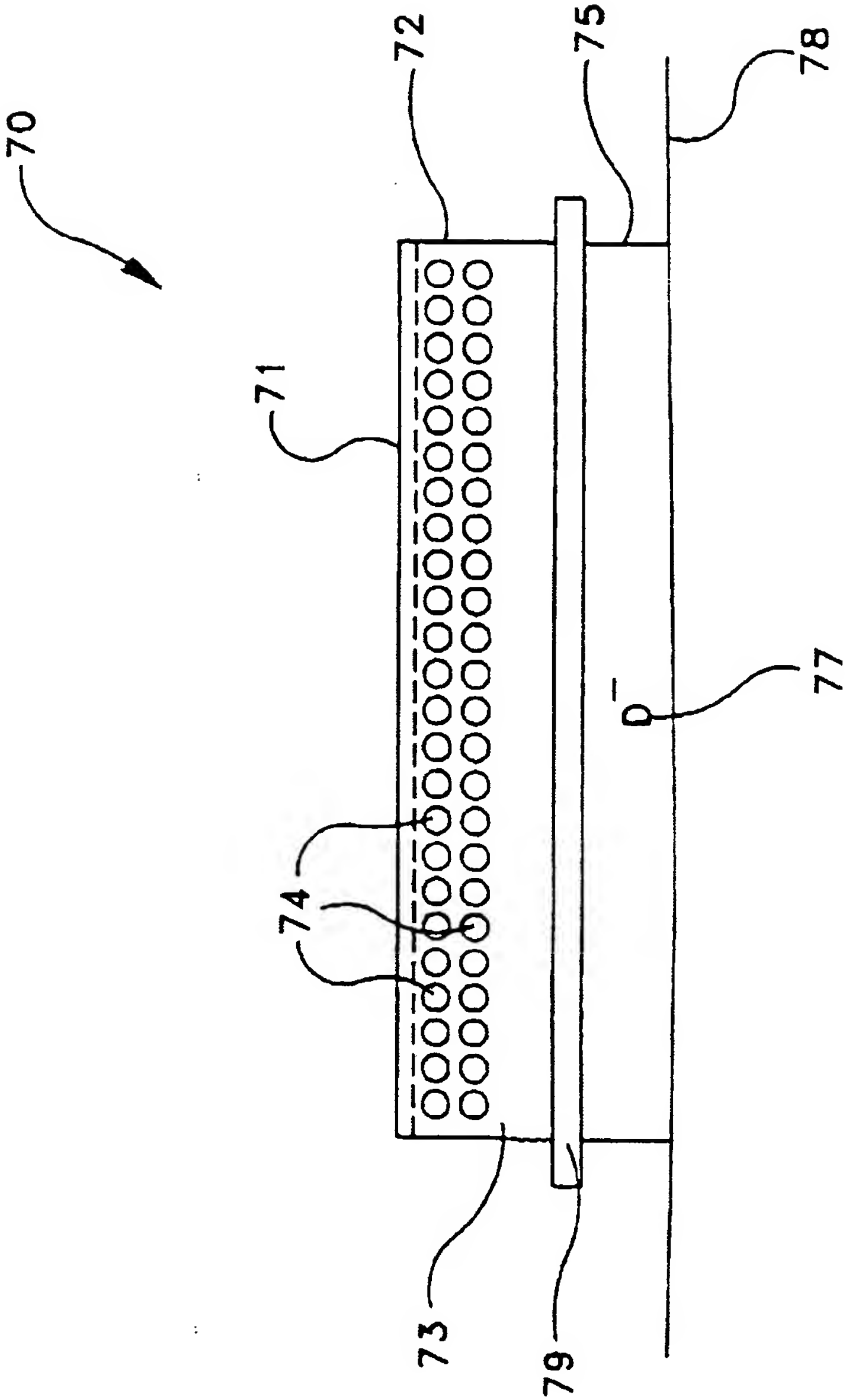


FIG-8

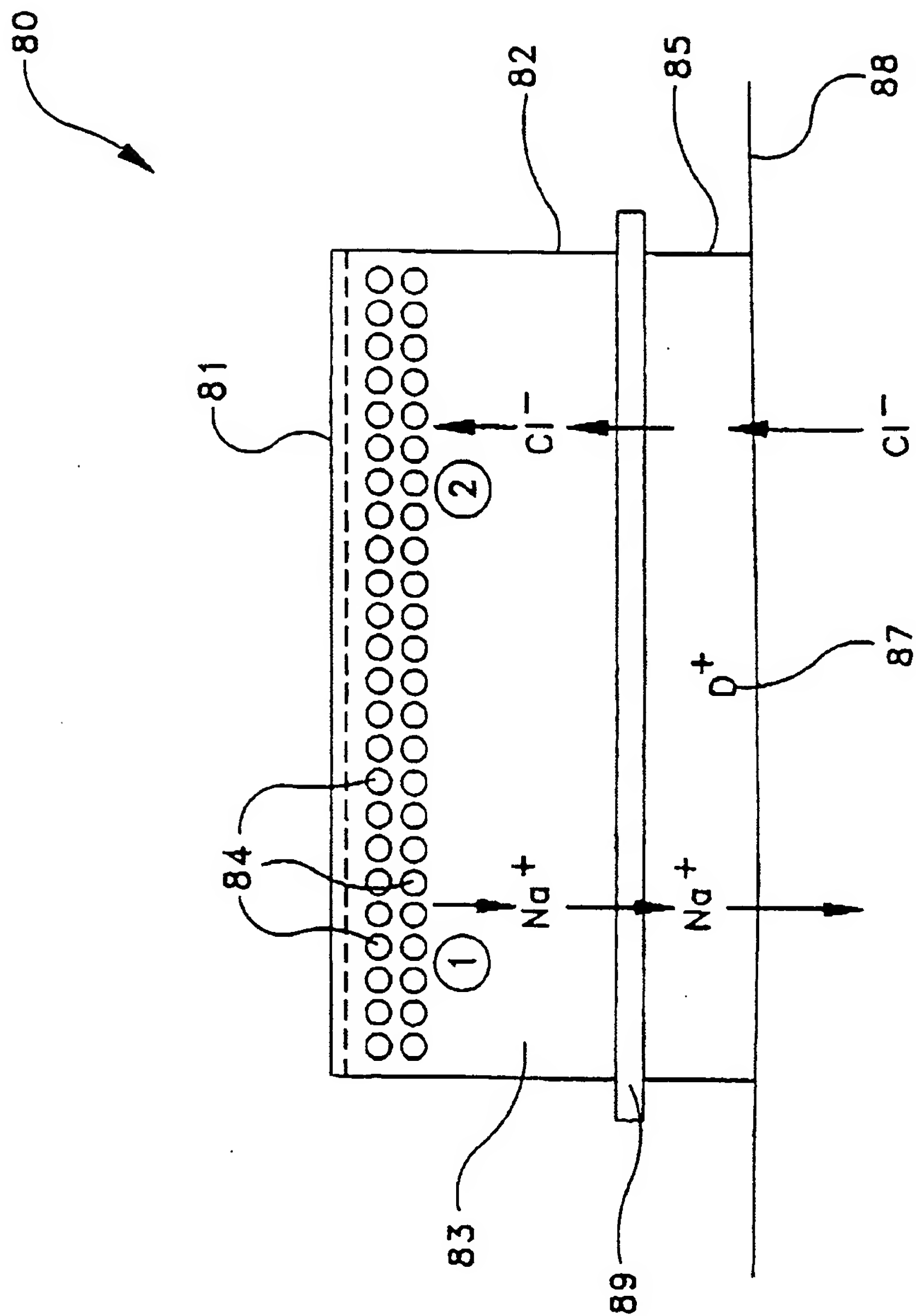
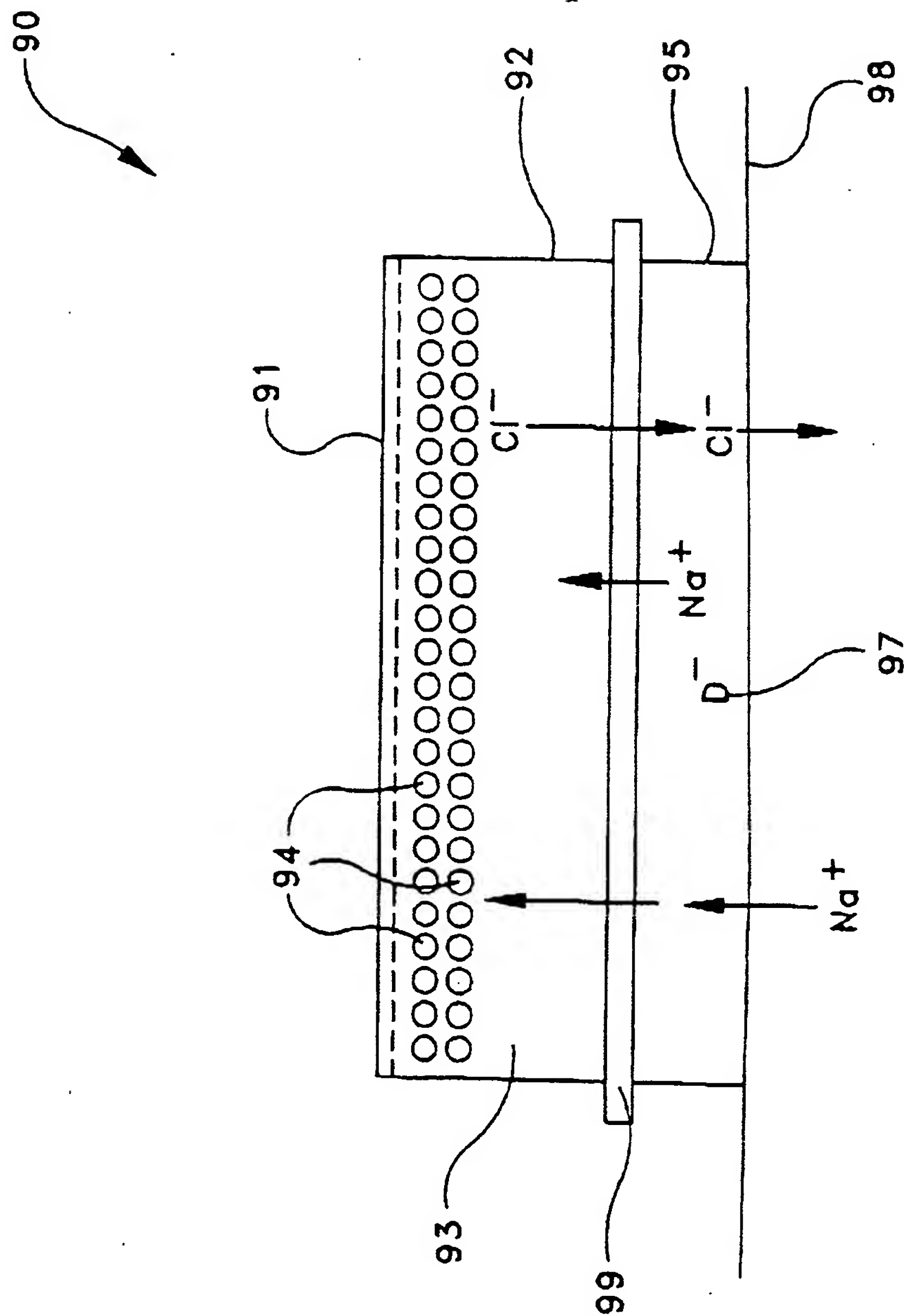


FIG-9



INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/IB 96/01081

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N1/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 16943 (ALZA CORP) 14 November 1991 see page 6, line 13 - page 10, line 23; figures	1-7, 15-21, 29-36, 50-56
A	--- US,A,4 927 408 (HAAK RONALD P ET AL) 22 May 1990 cited in the application see column 3, line 64 - column 12, line 68; figures --- -/--	1-7, 18-21, 26-36,56

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

14 February 1997

Date of mailing of the international search report

28.02.97

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INTERNATIONAL SEARCH REPORT

Inter. Application No.

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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